DRUG-INDUCED UPPER GASTROINTESTINAL BLEEDING – A REGIONAL STUDY

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Certificate

This is to certify that this dissertation entitled **"Drug-Induced Upper Gastrointestinal Bleeding - A Regional study",** is the bonafide record work done by **Dr.P.Subramanian** submitted as partial fulfillment for the requirements of M.D Degree Examination, General Medicine (Branch I) to be held in March 2008.

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List of abbreviations

1)	ARAMIS	-	**A**rthritis, **R**heumatism and **A**ging **M**edical **I**nformation **S**ystem
2)	CAHD	-	**C**oronary **A**rtery **H**eart **D**isease
3)	COPD	-	**C**hronic **O**bstructive **P**ulmonary **D**isease
4)	COX	-	**C**yclo **ox**ygenase
5)	EC	-	**E**nteric **C**oated
6)	EGF	-	**E**pidermal **G**rowth **F**actor
7)	FDA	-	**F**ood and **D**rug **A**dministration
8)	GI	-	**G**astro **I**ntestinal
9)	GIT	-	**G**astro **I**ntestinal **T**ract
10)	GPA	-	**G**astro-**P**rotective **A**gents
11)	H/O	-	**H**istory **O**f
12)	*H. pylori*	-	*Helicobacter pylori*
13)	hr.	-	**h**ou**r**
14)	H_2RA	-	**H**istamine-2 **R**eceptor **A**ntagonists
15)	NSAIDs	-	**N**on-**S**teroidal **A**nti-**I**nflammatory **D**rugs
16)	IgG	-	**I**mmuno**g**lobulin **G**
17)	IgA	-	**I**mmuno**g**lobulin **A**
18)	LP	-	**L**ipid **P**eroxidation
19)	mg	-	**m**illi **g**ram
20)	ml	-	**m**illi **l**iter
21)	NO	-	**N**itric **O**xide
22)	OTC	-	**O**ver-**T**he-**C**ounter
23)	PGE2	-	**P**rosta**g**landin **E2**
24)	PPI	-	**P**roton **P**ump **I**nhibitor
25)	PUD	-	**P**eptic **U**lcer **D**isease
26)	SR	-	**S**ustained **R**elease
27)	SSI	-	**S**erious **S**ystemic **I**llnesses
28)	SSRIs	-	**S**elective **S**erotonin **R**euptake **I**nhibitors
29)	TGF	-	**T**ransforming **G**rowth **F**actor
30)	UGI	-	**U**pper **G**astro**i**ntestinal

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Abstract

Study Objective: To study the clinical profile and risk factors in fifty cases of drug-induced UGI bleeding.

Design and Setting: Prospective study, Thanjavur Medical College hospital.

Patients: Fifty patients admitted with drug-induced hematemesis and/or malena.

Study period: Between March 2006 and August 2007.

Results: Prevalence of risk factors among the patients suffering from drug-induced UGI bleeding are as follows: [1] Old age $\geq$ 50 years of age - 66% [2] 'O' Blood group – 50% [3] Alcoholism – 42% [4] Not using Gastro protective agents – 40% [5] Self medication / OTC drugs – 36% [6] Smoking – 30% [7] Stress and Serious systemic illnesses – 12% [8] Helicobacter pylori – 12% [9] Known Peptic ulcer disease – 10% [10] High doses / Chronic drug intake – 10% [11] Concomitant use of Steroids – 8% and [12] Concomitant use of anticoagulants – 4%.

Conclusion: NSAIDs were the causative drugs for UGI bleeding in all the fifty cases studied. All those fifty cases had at least one known risk factor and majority (80%) had more than one risk factors of drug-induced UGI bleeding.

Keywords: UGI bleeding, NSAID, hematemesis, malena, PUD and H.pylori

CHAPTER - 1 INTRODUCTION

- International scenario
- National scenario

It is highly unfortunate that many patients are admitted daily with hematemesis and/or malena due to the adverse effects of drugs either prescribed or self medicated. Incidence of such cases can be greatly reduced if medical practitioners are not only aware of the adverse effects of drugs on gastrointestinal tract but also assess the patients for the risk factors of drug-induced UGI bleeding before prescribing these drugs and also by properly educating the patients. Non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin are among the most frequently prescribed drugs worldwide and are available 'Over-The-Counter' (OTC) also. Though reasonably safe in most cases in prescribed dosages and for short durations, these drugs cause serious gastrointestinal toxicity in a large number of cases, particularly in older age, history of peptic ulcer disease, alcoholism, smoking, stress, poor general health and concurrent use of steroids and anticoagulants. They can affect all segments of the gastrointestinal tract causing ulcers, severe bleeding, perforation, and obstruction. It is therefore imperative for physicians to be aware not only about their serious adverse effects but also about the risk factors of drug-induced gastrointestinal (GI) bleeding and use these drugs with caution and only when genuinely indicated.

1.1 International scenario

World over, 35 million people consume NSAIDs including aspirin on a daily basis, and about 30% of these users may develop GI toxicity of sufficient degree requiring a physician's intervention. Conservative calculations estimate that approximately 1, 07,000 patients are hospitalised annually

for NSAID-related gastrointestinal complications, and at least 16,500 NSAID- related deaths occur each year among arthritis patients alone. Surprisingly, the management of this problem has undergone little change in the past 50 years, and is not only frequently under-diagnosed but also under-treated (Vikas *et al.,* 2003).

There were approximately 11.14 crore NSAID prescriptions in the United States for the year ending in August 2000 (Retail and Provider Perspective, 2000). In addition, annual United States sales of over-the-counter oral analgesics approach three billion dollars; The prevalence of at least once-weekly NSAID use among people 65 years old or older has been reported to be as high as 70%; half of this group takes at least seven doses a week (Talley *et al.,* 1995; Loren, 2001).

Based on an analysis of acute hospital admissions in one health district in United Kingdom, it has been calculated that NSAID-related upper GI events account for around 12,000 admissions annually in England and result in approximately 2500 potentially avoidable deaths each year. Most of the dead were taking higher doses of NSAIDs for long duration or elderly or chronic alcoholic or known peptic ulcer disease patients (Belsey, 2003).

Each year, use of NSAIDs accounts for an estimated 7,600 deaths and 76,000 hospitalisations in the United States (Fries, 1992) and for 365 deaths and 3897 hospitalisations in Canada (Griffin *et al*., 1991; Statistics Canada 1992). One percent to three percent of NSAID users have gastrointestinal bleeding. It has also been estimated that one third of the cost of treating arthritis patients relates to treatment of the side effects of NSAIDs. Older age, history of peptic ulcer disease, higher NSAID dose, alcoholism and concurrent use of corticosteroids and anticoagulants increase the risk for

serious gastrointestinal side effects. Almost all deaths from NSAID related gastrointestinal side effects occur in elderly persons; elderly women seem particularly susceptible (Robyn *et al.,* 1997).

1.2 National scenario

Indian studies have shown that NSAIDs including aspirin are among the most common drugs responsible for adverse drug reactions seen in clinical practice. In general, at least 10 to 20 percent of patients have dyspepsia while taking an NSAID, although the prevalence may range from 5 to 50 percent.

Incidence of new ulcer cases following NSAID intake, ranges from 10% to 40% for gastric ulcers and 5% - 15% for duodenal ulcers. Most patients are, however, asymptomatic (Simon *et al.,* 1999). Seventy percent of the patients admitted with drug induced UGI bleeding were $\geq$ 50 years of age (Vikas *et al.,* 2003).

According to prospective data from the Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS), 13 of every 1,000 patients with rheumatoid arthritis who take NSAIDs for one year have a serious gastrointestinal complication (Singh, 1998; Simon *et al.,* 1999). In India, quacks also practice these drugs commonly and elderly are the most affected (Vikas *et al.,* 2003).

* * *

CHAPTER - 2 AIM OF THE STUDY

- Aim of the study

2.1 Aim of the study

- To study the clinical profile of patients admitted with drug-induced upper gastrointestinal bleeding.

- To find out the risk factors for the drug-induced UGI bleeding in those patients.

- To find out the prevalence of the risk factors among them.

* * *

CHAPTER - 3 LITERATURE REVIEW

- Gastric mucosal barrier
- Drugs causing UGI Bleeding
- Mechanisms of drug-Induced UGI Bleeding
- Clinical and endoscopic features of drug-induced gastrointestinal damage
- Sustained release and enteric coated NSAIDs
- COX-2 selective inhibitors
- Risk factors of drug-induced UGI bleeding
- Management of drug-induced UGI bleeding

Peptic Ulcer Disease (PUD) results from the imbalance between the defensive factors that protect the mucosa and offensive factors that disrupt the important gastric mucosal barrier. Many of the primary ulcers seen in teenagers are now thought to be associated with *Helicobacter pylori* infection while many of the secondary ulcers are due to use of NSAIDs including aspirin.

3.1 Gastric mucosal barrier

The gastric mucosal barrier is composed of several hierarchically organized anatomical and functional components, which mutually contribute to the mucosal integrity endangered by the offending luminal acid. The barrier consists of three protective components (Source: http://en.wikipedia.org/wiki; Last accessed 9 September 2007). The three components include:

(1) A compact epithelial cell lining

Cells in the epithelium of the stomach are bound by tight junctions that repel harsh fluids that may injure the stomach lining. The surface epithelial cell layer has properties of easy desquamation, rapid regeneration, and production of bicarbonate and phospholipid surfactant. The apical cell membrane and the very tight gastric surface mucosal tight junctions are generally resistant to acid back-diffusion and may serve further to retard hydrogen ion back-diffusion.

(2) A special mucus covering

Derived from mucus secreted by surface epithelial cells and mucosal neck cells this gel-like coating protects the entire surface of the gastric mucosa from auto digestion by e.g. pepsin and from erosion by acids and other caustic materials that are ingested. The mucus gel contained numerous phospholipids, and its luminal surface was coated with a film of phospholipid - a surfactant layer which accounts for the remarkably strong hydrophobic nature of the gastric luminal surface, which, in turn, provides protection against damaging agents. Physico-chemical effect of the very high viscosity of the mucus layer and its ability to retain bicarbonate secreted by the epithelium with maintenance of a pH gradient is also an important factor in protection.

The protective properties of prostaglandins are not based only on their antisecretory but also on their cytoprotective action. They stimulate glycoprotein and bicarbonate secretion and enhance the microcirculation, cellular oxygen supply, restitution and repair (Robert *et al.*, 1979).

(3) Bicarbonate ions

The bicarbonate ions are secreted by the surface epithelial cells of the stomach and duodenum. The pre-epithelial mucus-HCO_3 layer buffers back diffusing luminal H^+ preventing its entry inside the epithelial cells.

The peptides epidermal growth factor (EGF) and transforming growth factor-alpha (TGF-alpha) have potential role in barrier maintenance by binding to a common receptor and stimulate epithelial cell proliferation. In the stomach, they also enhance mucus secretion and inhibit acid

production. Cytokines such as fibroblast growth factor and hepatocyte growth factor are found to enhance healing of gastrointestinal ulcers in experimental models (Murphy, 1998).

Trefoil proteins are a family of small peptides that are secreted abundantly by goblet cells in the gastric and intestinal mucosa, and coat the apical face of the epithelial cells and render them resistant to proteolytic destruction. Trefoil peptides play an important role in mucosal integrity, repair of lesions, limitation of epithelial cell proliferation and protection of the epithelium from a broad range of toxic chemicals and drugs.

Nitric oxide (NO) plays a crucial role in mucosal integrity and barrier function with stimulation of fluid and mucus secretion, enhancement of microcirculation and maintenance of epithelial barrier function. It is synthesized from arginine through the action of nitric oxide synthease (NOS). In several models, co-administration of NO donors such as glyceryltrinitrate and NSAIDs results in anti-inflammatory properties comparable to NSAIDs alone, but with less damage to the gastrointestinal mucosa (Muscara, 1999). Several studies have emphasized the roles of NOsynthase (NOS) and COX in maintaining gastric mucosal integrity and epithelial restitution (Wallace and Granger, 1992).

3.2 Drugs causing UGI bleeding

Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) **(Table 3.1)** are responsible for most drug-induced GI bleeding. The elderly are especially susceptible to NSAID-induced GI bleeding. NSAIDs may cause bleeding at any level of the GI tract, but they most commonly do so in the

stomach or duodenum. Although the bleeding risk increases in proportion to NSAID dose, any amount (including low-dose aspirin taken for cardiovascular prophylaxis) may cause bleeding particularly when taken on empty stomach. Use of selective serotonin reuptake inhibitors (SSRIs) has recently been found to be associated with a higher risk of upper GI bleeding, especially in patients who are also taking NSAIDs or low-dose aspirin (Dalton *et al.,* 2003). Alendronate and potassium chloride also cause upper GI bleeding in very few cases. Role of steroids in ulcerogenesis is relatively small, although hemorrhage seems to be the most common complication from peptic ulcers in steroid-treated patients (Messer *et al.,* 1983; Fadul *et al.,* 1988). Anticoagulants do not cause GI bleeding per se, but they can unmask or aggravate hemorrhage from preexisting lesions (Dalton *et al.,* 2003).

Table 3.1 Classification of NSAIDs

Non-steroidal anti-inflammatory drugs	
Salicylates	Aspirin (Acetylsalicylic Acid), Diflunisal, Ethenzamide, Salicin
Arylalkanoic acids	Diclofenac, Etodolac, Indometacin, Nabumetone, Sulindac
2-Arylpropionic acids (profens)	Carprofen, Flurbiprofen, Ibuprofen, Ketoprofen, Ketorolac, Loxoprofen, Naproxen, Oxaprozin, Suprofen, Tiaprofenic acid
N-Arylanthranilic acids (fenamic acids)	Mefenamic acid
Pyrazolidine derivatives	Phenylbutazone
Oxicams	Meloxicam, Piroxicam
Coxibs	Celecoxib, Etoricoxib, Parecoxib, Rofecoxib, Valdecoxib, Lumiracoxib
Sulphonanilides	Nimesulide
Topically used products	Diclofenac, Flurbiprofen, Ibuprofen, Indomethacin, Ketoprofen, Naproxen, Piroxicam, Suprofen

3.3 Mechanisms of drug-induced UGI bleeding

Prostaglandins protect GI mucosa by forming a cytoprotective layer and increasing the secretion of bicarbonate ions that neutralise the gastric acidity. All therapeutically useful NSAIDs act by inhibiting the synthesis of PGs (Tamblyn, 1997). NSAIDs-induced inhibition of prostaglandin biosynthesis has resulted in an enhanced production of leukotrienes and other products of the 5- lipoxygenase pathway (Whittle *et al.,* 1993). These products alter the mucosal barrier with an increased gastric mucosal permeability for H+ ions and Na+ ions and reduced transmucosal potential difference thereby promoting the formation of erosions and ulcers (Kubes *et al.,* 1991; Jimenez *et al.,* 2002). The hydrophobic acid-resistant property of the gastric surface active phospholipid layer (SAPL) is rapidly attenuated by NSAIDs. Secretion of bicarbonate ions also is inhibited by NSAIDs (Knutson and Flemstrom, 1989; Isenberg and Flemstrom, 1991).

Cyclooxygenase has two isoforms, one constitutive (COX-1) and another inducible (COX-2). A third isoform (COX-3) has recently been described as well. COX-1 is responsible for production of prostaglandins which are essential for maintenance of normal endocrine and renal function, gastric mucosal integrity and haemostasis. In contrast, COX-2 is virtually undetectable in most tissues, but the enzyme activity may be dramatically up regulated by inflammatory and mitogenic stimuli (Dequeker *et al.,* 1998). Conventional NSAIDs cause non-selective inhibition of cyclooxygenase, which leads to reduction in bicarbonate secretion and reduced mucous production. Coupled with it is vasoconstriction that occurs due to NSAIDs, which causes hypoxia and consequent formation of ulcer. COX-2 selective inhibitors appear not to be ulcerogenic. Most NSAIDs are

weak organic acids and have low pKa. Therefore, they remain unionised in stomach and are absorbed appreciably from stomach. However, once they breach the cell membranes of stomach cells and reach within, they encounter a basic pH (e.g. 7.1). This causes so called 'trapping' of the drugs inside the cell (Raskin, 1999). This topical effect is considered an important mechanism of gastro-duodenal damage associated with their use. Even short-term (<1 week) use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) can precipitate ulcer-related bleeding. Thus, it can be understood to be the disease of the war between the factors favoring and those opposing the development of ulcers where the former win over the latter.

Aspirin, the only NSAID able to irreversibly inhibit COX-1, also shows inhibition of platelet aggregation because it inhibits the action of thromboxane-A. Aspirin also causes capillary fragility, increased fibrinolysis and a prolonged bleeding time. Role of steroids in ulcerogenesis is small and anticoagulants do not cause GI bleeding per se, but both can aggravate hemorrhage from preexisting ulcers.

The risk of NSAID induced GI ulcer development is increased in patients with advanced age, positive family history, female sex, prolonged use of high dose of NSAIDs and concomitant use of anticoagulant drugs and gastrotoxic drugs like steroids, Hepatic-renal dysfunction, alcoholism, heavy coffee consumption, *H pylori* infection and poor general health (Simon *et al.,* 1999).

3.4 Clinical and endoscopic features of drug-induced gastrointestinal damage

NSAIDs-induced GI damage is of three main types:

- Superficial damage such as mucosal hemorrhages and erosions.
- Endoscopically documented non-symptomatic ('silent') ulcers.
- Symptomatic ulcers causing complications such as GI hemorrhage.

NSAIDs including aspirin induced ulcers are usually symptom less unless complicated. Early symptoms are mild and benign like dyspepsia, nausea, vomiting, and anorexia. Pain is usually a late feature. When the ulcer starts bleeding hematemesis and/or malena occurs in about 1 to 3 % of patients. Most cases of NSAID-induced gastrointestinal ulcers can heal spontaneously, even when the drug is continued (Vikas *et al.,* 2003). Moreover, it is not usually possible to diagnose these ulcers on the basis of clinical features alone, as symptoms suggestive of the ulcers can occur frequently in their absence. Elderly patients usually have painless gastric ulceration and NSAIDs can mask the symptom of pain (Dhikav, 2001). In fact, most elderly patients are referred to physicians for iron deficiency anemia due to fecal blood loss.

Few features **(Box 3.1)**, however, can be suggestive of NSAID-induced ulceration – like absence of *H.pylori* infection, anorexia rather than abdominal pain, antral location of gastric ulcers, known risk factors and prolonged self-medication of the large doses of NSAIDs. Chronic NSAID use can increase the risk of ulcer development by 10-30 folds (Andrade *et al.,*

1999; Yeoman, 2001). Elderly patients are particularly prone to develop GI toxicity and unfortunately they are the most frequent users of this group of drugs (Yeoman, 2001).

Box 3.1 Features of NSAID induced GI ulcers

- More than 3 mm in size
- Deep lesions
- Prone to complications like bleeding, perforation and obstruction
- Gastric or duodenal in location
- Multiple erosions (more than 10)
- Antral in location
- Absence of H.pylori

3.4.1 Oesophagus

Prolonged use of aspirin and most NSAIDs can result in ulceration, oesophagitis and even strictures more commonly caused by reflux rather than direct action of NSAIDs.

3.4.2 Stomach and duodenum

The features of NSAID ingestion and injury in the stomach and duodenum in acute and chronic cases are given in the following **Table 3.2** and UGI endoscopic view of naproxen induced duodenal ulcer is given as **Figure 3.1.**

Table 3.2 NSAID ingestion and GI injury

Injury type	*Gastro-duodenal lesion*	*Frequency*
Acute (1-2 weeks)	mucosal erythema, superficial erosions, submucosal haemorrhage, Increased fecal blood loss	60-100%
Chronic (> 4 weeks)	gastric antral erosions and ulcers, duodenal Ulcers and erosions	5-30%

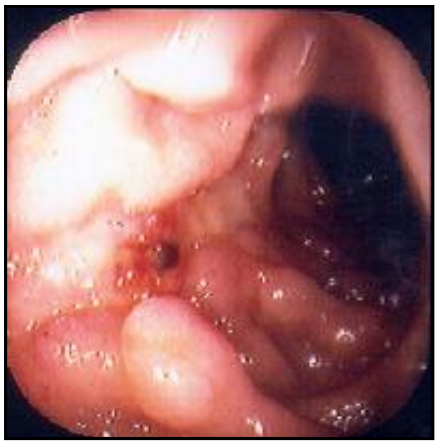

Figure 3.1 Naproxen induced duodenal ulcer

3.4.3 Small intestine

Ulceration of small intestine other than duodenum has historically been difficult to study. One endoscopic study found a prevalence of 26% in patients taking these drugs on long-term basis and presenting as cases of occult blood loss (Morris *et al.,* 1991). In small intestine, serious lower GI events occurred at a rate of 0.9% per year in rheumatoid arthritis patients taking non-selective NSAIDs, accounting for 40% of the total adverse GI

events in these cases (Loren, 2003). A number of studies suggest that ulceration and perforation in small intestine is related to slow release and enteric coated formulations of NSAIDs and aspirin (Bjarnason *et al.,* 1987). Syndrome of occult blood loss, malabsorption, anemia, and protein losing enteropathy has been described in many cases (Gibson *et al.,* 1992).

3.4.4 Large intestine, rectum and anal region

There are only a few cases of NSAID induced damage in this segment of GIT. In colon and ano-rectal area they cause colitis, proctitis, and presentation similar to inflammatory bowel disease, bleeding (both acute and chronic), ulcers, and strictures. Most ulcerative complications like perforation are seen in caecum (Carlson *et al.,* 1990). Rectal suppositories can result in proctalgia, tenesmus, or watery diarrhoea. Approximately, 10 - 30% cases can develop these problems (Kurahur *et al.,* 2001).

Arthritis, rheumatism, and ARAMIS study which has prospectively followed patient status and outcomes, drug side effects, and the economic impact of illness for > 11,000 arthritis patients at eight participating institutions in the United States and Canada (Simon *et al.,* 1999) shows that [1] osteoarthritis and rheumatoid arthritis patients are 2.5 - 5.5 times more likely than the general population to be hospitalised for NSAID related GI events; [2] the absolute risk for serious NSAID-related GI toxicity remains constant and the cumulative risk increases over time; [3] there are no reliable warning signals (> 80% of patients with serious GI complications had no prior GI symptoms); [4] independent risk factors for serious GI events were age, prednisolone use, NSAID dose, disability level, and previous NSAID-induced GI symptoms; and [5] antacids and H_2 antagonists

do not prevent NSAID-induced gastric ulcers (Doomra and Gupta, 2001; Simon *et al.,* 1999).

3.5 Sustained release and enteric coated NSAIDs

Studies have demonstrated increased intestinal permeability with SR and EC formulations of all NSAIDs but not with conventional release tablets and lower GI bleeding are also more common with them (Choi *et al.,* 1995). These formulations claim to cause fewer adverse effects than the conventional formulation and that they could be prescribed for patients who are most prone to develop such adverse effects. This phenomenon has been termed 'channeling' and may complicate any interpretation of the epidemiology of adverse effects (Leufkens *et al.,* 1992). These lesions are often difficult to diagnose on enteroscopy, colonoscopy and barium scans as radiological findings can be subtle and easily missed. The prescribing of SR NSAID formulations to patients with pre-existing bowel disease (i.e., diverticulitis, inflammatory bowel disease) and physiological conditions that lead to delayed transit (stenosis, anticholinergic drugs, diverticuli) may represent relative or absolute contraindications to such formulations and require special clinical considerations (Neal, 1999). Colonoscopic view of sustained release diclofenac induced ulcer is shown below in **Figure 3.2.**

Figure 3.2 Sustained release tablet diclofenac induced colonic ulcer

3.6 COX-2 selective inhibitors

These newer NSAIDs do not inhibit COX-1 and, therefore, do not have the disadvantage of reducing the synthesis of protective prostaglandins. Selective COX-2 inhibitors are associated with, at best, a modest decrease in the risk of ulcer bleeding. One study showed that the combination of a traditional NSAID with a daily proton pump inhibitors (PPI) had the same risk of bleeding as that of a COX-2 inhibitor alone (Chan, 2002). One potential clinical advantage to using a coxib rather than an NSAID-PPI combination involves the prevention of lower GI bleeding (Schnitzer *et al.,* 2004). In patients taking COX-2 inhibitors, clinical events were less by 54%, signifying that these drugs were half as likely to cause adverse events as compared to conventional drug (Loren, 2003).

3.7 Risk factors of drug-induced UGI bleeding

3.7.1 Old age

Elderly patients are particularly prone to develop drug-induced GI toxicity and unfortunately they are the most frequent users of this group of drugs (Yeoman, 2001). The elderly patients are deficient in cytoprotective prostaglandins (PGE2 and PGI2) that increase mucous production and improve ulcer healing. Moreover, the vascular integrity of the ulcer base is poor; therefore, ulcers bleed easily in elderly patients (Dhikav, 2001; Dhikav *et al.,* 2002). Osteoarthritis, lumbago, arthralgia, spondyloses, rheumatoid diseases and ischemic cardiac diseases are the major indications to prescribe NSAIDs and aspirin. Elderly patients usually have painless gastric ulceration and NSAIDs can mask the symptom of pain (Dhikav, 2001). Almost all deaths from NSAID related gastrointestinal side

effects occur in elderly persons and elderly women seem particularly susceptible (Robyn *et al.,* 1997)**.** Elderly are at the greatest risk for drug-induced UGI bleeding and the relative risk at 65 - 74 year age group is 3.8 times that in the general population (Griffin *et al.,* 1991).

3.7.2 High doses / Chronic drug intake

Chronic NSAID use can increase the risk of ulcer development by 10 - 30 folds. Chronic aspirin use even in low doses (≤ 150 mg) for conditions such as cardiovascular prophylaxis causes substantial GI toxicity and patients may present with iron deficiency anaemia as chronic use of aspirin can cause up to two litres of the blood loss over years (Andrade *et al.,* 1999; Yeoman *et al.,* 2001). There is a three-fold increase in the risk for dyspepsia in populations consuming high doses of NSAIDs with a four-fold increased risk for ulcer (Hawkey, 2000; Ofman *et al.,* 2003). They are also responsible for a number of peptic ulcer complications such as bleeding and perforation. Severe ulcer complications occur in 5% of chronic NSAID users (Halter *et al*., 2001). The risk of bleeding increases with incremental doses of NSAIDs, especially ibuprofen, diclofenac and piroxicam (Singh, 1999).

3.7.3 Self medication / OTC drugs

All NSAIDs including aspirin are now available ‘over the counter’. Patients who are unaware of the adverse effects of these drugs, particularly the elderly and poorly educated people frequently take these drugs on long term. Sometimes, they take these drugs along with prescribed drugs like NSAIDs including aspirin, steroids and anticoagulants and occasionally on

empty stomach. In India, quacks also practice these drugs commonly and elderly are the most affected (Vikas *et al.,* 2003).

Approximately 70 million NSAID prescriptions are written annually in the USA and 30 million are dispensed over-the-counter (Graumlich, 2001). A large study involving 421 patients admitted to a hospital in UK with upper gastrointestinal haemorrhage, who took NSAIDs, revealed that non-prescription drug use was an important cause of bleed. The most common sites of bleeding in that study were gastric ulcers (31%) and duodenal ulcers (26%). Therefore, attempts should be made to discourage people from taking these drugs on nonprescription basis, especially over a long term without clinical supervision (Hawkey *et al.,* 1998; Graham *et al.,* 2002). Review of post-marketing case reports collected by the FDA's Adverse Event Reporting System (AERS) between 1998 and 2001 identified a total of 279 cases of GI bleeding in the United States associated with the otc use of NSAIDs: 197 cases for ibuprofen, ketoprofen and naproxen, and 82 cases for aspirin.

3.7.4 Use of Gastro protective agents

Gastro protective agents (GPAs) are often co-prescribed with NSAIDs, with the aim to reduce the associated GI adverse effects. Co-prescribing rates range from 17 to 34% in the literature (Rogind, 1997).

Studies have found significant interactions ($P < 0.001$) between ulcer healing drugs and each type of NSAIDs. All the interaction ratios were less than 1.0, indicating that the risk of adverse gastrointestinal events

associated with taking non-steroidal anti-inflammatory drugs is lower in patients also taking ulcer healing drugs than in patients not taking ulcer healing drugs (Hooper *et al.,* 2004).

The most commonly used GPAs include proton pump inhibitors (PPI), H_2 receptor antagonists (H_2RA), antacids and misoprostol. Although these agents have shown to be efficacious to certain extent in prophylaxis and treatment of NSAID related GI events, they are not without additional side effects and they have cost implications also. Parenteral PPIs are the most efficacious of all gastroprotective drugs. Misoprostol has shown to reduce the serious upper GI complications by almost 40% (Schnitzer *et al.,* 1995), but is poorly tolerated because of its own side effects, mainly diarrhoea and abdominal pain. Omeprazole is currently the only PPI licensed for both healing and prophylaxis of NSAID-associated ulcers, and usually better tolerated than misoprostol (Williams *et al.,* 1989).

3.7.5 Known PUD

Patients with previous H/O complicated or uncomplicated ulcers are reported to have the highest absolute risk (around 38.5) for UGI bleeding (Lucker *et al.*, 1994). The VIGOR study (Paulsen *et al.*, 1991) involving over 8,000 patients, has reported the relative risk of having a GI event as 4.0 for patients with prior UGI events. Patients with past history of peptic ulcer disease are having the highest risk to develop NSAID induced ulcer bleeding (Loren, 2003).

3.7.6 Alcoholism

Ethanol, a well established 'barrier breaking agent', increases mucosal permeability by enhancing the conductance of apical Na^+ and basolateral K^+ channels in surface epithelial cells. There is growing evidence that lipid peroxidation (LP) could play a significant role in the pathogenesis of ethanol-induced gastric mucosal lesions, especially because oxygen radicals have been directly implicated in the damage of cell membranes after administration of alcohol (Szelenyi and Brune, 1988; Terano *et al.,* 1989; Kvietys *et al.,* 1990). In a 20 year period the ratio of acute bleedings related to ulcers (Gastric ulcer+Duodenal ulcer) decreased from 69% to 50%, twofold increase in frequency of drug induced acute bleedings (17% vs. 35%) and the ratio of alcohol related bleedings was threefold higher in 2003 than in the '80s (Gy Pécsi and Rácz, 2004). As the quantity of alcohol consumption increased, the relative risk of upper GI bleeding also increased, up to a relative risk of 2.8 in heavy alcohol consumers (Kaufman *et al.,* 1999).

3.7.7 Smoking

Smoking increases acid secretion, reduces prostaglandin and bicarbonate production, accelerates gastric emptying and decreases mucosal blood flow, all favouring ulcerogenesis. It is suggested that, at least in men, chronic smoking increases maximal gastric secretion, and therefore could have a role in the etiology of duodenal ulcer. Smoking is found to be associated with a threefold elevation in the risk of UGI bleeding in patients taking NSAIDs compared with no smoking (Peura, 2004). Ulcer healing with

H_2 receptor antagonists is significantly delayed in smokers compared to non smokers. Also the relapse rate of duodenal ulcer is higher in smokers compared with non smokers (Korman *et al*., 1981).

3.7.8 Stress and Serious systemic illnesses

The foremost effect of stress on the gastrointestinal tract is to decrease mucosal blood flow and altered gastric luminal acidity and thereby compromises the integrity of the mucosal barrier. Reduced mucosal blood flow suppresses production of mucus and limits the ability to remove back diffusing protons. As a consequence, significant stress is almost always associated with mucosal erosions, particularly in the stomach. A majority of these lesions are sub clinical, but gastrointestinal hemorrhage and sepsis are not infrequent consequences (Thompson, 1995).

Stress gastritis and mucosal ulceration are historically associated with (1) head injuries with associated elevations in intracranial pressure (Cushing ulcer), and (2) burn injuries (Curling ulcer). In critically ill ventilated patients, stroke, renal failure, respiratory failure, cardiac dysfunction, and coagulopathy disorder were associated with increased risk of significant gastrointestinal bleeding whereas enteral nutrition and stress ulcer prophylaxis with ranitidine decreased gastrointestinal bleeding (Sprit, 2003; Martindale, 2005).

Patients suffering from shock, sepsis, massive burns, severe trauma, or head injury can develop acute erosive gastric mucosal changes or frank ulceration with bleeding. Classified as stress-induced gastritis or ulcers, injury is most commonly observed in the acid-producing (fundus and body) portions of the stomach. The most common presentation is gastrointestinal

bleeding, which is usually minimal but can be life-threatening. Endoscopic studies have demonstrated that such lesions may occur within hours of admission to the ICU. About 75 – 100% of ICU patients will have endoscopic lesions within 24 hours, but only a small percentage develop stress related gastric bleeding (Goldin and Peura, 1996). Overt bleeding, generally defined as the occurrence of hematemesis, gross blood or 'coffee grounds' in the nasogastric aspirate, haematochezia or malena, occurs in 5 – 25% of ICU patients (Cook, 1991; Mutlu, 2001). Clinically significant bleeding, generally defined as bleeding requiring therapy, overt bleeding complicated by hemodynamic instability or a drop in hemoglobin, and transfusion of two units of blood within 24 hours, occurs in only 1.5 – 2.6% of critically ill patients (Cook *et al.,* 1991). In the ICU patients with UGI bleeding, 23.95% had respiratory failure, 19.79% had CNS problems and 16.79% had cardiovascular dysfunction, 12.27% had Sepsis (Manucherhr, 2007). The risk of bleeding is about 75% in the first two weeks of ICU patients (Deborah *et al.,* 1999). Prolonged mechanical ventilation, renal failure and coagulopathy are the most important predictors of stress ulcer related bleeding (Deborah *et al.,* 2001).

3.7.9 Concomitant use of other gastro toxic drugs

Glucocorticoids lead to atrophy of all epithelial tissues including gastro intestinal mucosa. Their role in ulcerogenesis is relatively small. Haemorrhage in steroid takers is related to duration of therapy and dose. Although hemorrhage seems to be the most common complication from peptic ulcers in steroid-treated patients (Messer *et al.,* 1983; Fadul *et al.,* 1988), gastroduodenal perforation is also a well-recognized complication

attributed to the use of corticosteroids (Koness *et al.,* 1990; Gunshefski *et al.,* 1990; Bodner *et al.,* 1990) leading to diffuse peritonitis.

Association between perforation of colonic diverticula and corticosteroids is more underappreciated (Corder, 1987; Arsura, 1990; Chan *et al.,* 1992; Weiner *et al.,* 1993). Corticosteroids cause thinning of the intestinal wall, diminution of the efficacy of host defenses, and inhibition of protective barriers thus increase the potential for the development of diverticulitis (Fadul *et al.,* 1988).

The lack of muscular layer in diverticula and the concomitant alteration in structural protein synthesis by corticosteroids would favor diverticular perforation (Arsura, 1990). Anticoagulants do not cause GI bleeding per se, but they can unmask or aggravate hemorrhage from preexisting lesions (Dalton *et al.,* 2003). Steroids and anticoagulants when combined with low doses of aspirin or non selective NSAIDs or COX-2 selective inhibitors they increase the chances of UGI bleeding many folds (Fabrice *et al.,* 1998).

3.7.10 'O' Blood group

The observation of a 'biological gradient' between the frequency of blood group '0' and susceptibility to peptic ulceration may be regarded as support for the hypothesis that the blood group substances play a direct part in the causation of the disease, or in protecting against it (Balint *et al*., 1957). Patients who do not secrete ABO antigens in their saliva and gastric juice are known to be at higher risk of UGI bleeding (Boren *et al.,* 1993). Boren and colleagues have concluded that blood group antigen mediates *H.pylori* attachment to human gastric mucosa. This study, focusing on a North American cohort, suggested that 'the availability of

Helicobacter pylori (*H.pylori)* receptors might be reduced in individuals of blood group A and B phenotypes, as compared to blood group 'O' individuals'. The large amount of information now available shows that stomal, duodenal and gastric ulcers are all commoner in persons belonging to blood group 'O' than in persons belonging to the other three blood groups.

3.7.11 Helicobacter pylori

Helicobacter pylori, **(Figure 3.3)** a helical shaped Gram-negative bacterium is the only known microorganism that can thrive in the highly acidic environment of the stomach. Its helical shape is thought to have evolved to penetrate and favor its motility in the mucus gel layer (Samuel, 1996). *H. pylori* can be found in the antrum of stomach in 95% of patients with a duodenal ulcer and in most patients with a gastric ulcer not associated with NSAID use.

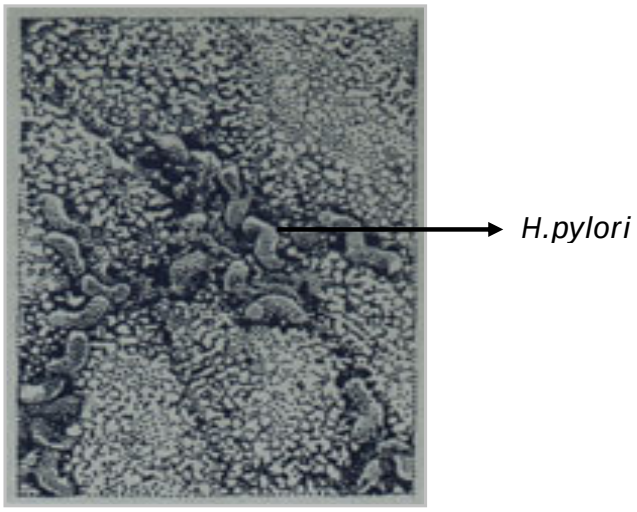

Figure 3.3 Electron microscopic picture of *H.pylori*

Survival of *H.pylori* in the acidic stomach is dependant on urease the enzyme which metabolizes urea (which is normally secreted into the stomach) to carbon dioxide and ammonia which neutralizes gastric acid. The ammonia that is produced is toxic to the epithelial cells, and with other products of *H.pylori*, including protease, catalase, and phospholipases, causes damage to those cells (Viala *et al.,* 2004). *Helicobacter* infection is associated with high levels of gastrin and pepsinogen and a significant reduction in somatostatin, gastric surface hydrophobicity and the phospholipid concentration of the oxyntic mucosa, all favoring ulcer formation (Lichtenberger *et al.,* 1997).

One can test non-invasively for *H.pylori* infection with a blood antibody test, stool antigen test, or with the carbon urea breath test (in which the patient drinks ^{14}C- or ^{13}C-labelled urea, which the bacterium metabolizes producing labelled carbon dioxide that can be detected in the breath). However, the most reliable method for detecting *H .pylori* infection is a biopsy check during endoscopy with a rapid urease test, histological examination, and microbial culture. Enzyme Linked Immuno Sorbent Assays (ELISA) can detect both immunoglobulin G (IgG) and immunoglobulin A (IgA) antibodies directed against *H. pylori*.

The sensitivity of most serologic tests is approximately 95%. Commercial ELISA detecting anti *H.pylori* serum IgG are the serologic tests of choice for the primary screening of patients with uncomplicated infections (Laheji *et al.,* 1998). Although initially controversial, most evidence now supports the assertion that *H. pylori* and NSAIDs are synergistic with respect to the

development of PUD. Eradication of *H.pylori* in the setting of chronic NSAID use is associated with a decreased risk of ulcer bleeding (Lai, 2002).

A meta-analysis found that *H.pylori* eradication in NSAID-naive users prior to the initiation of NSAIDs was associated with a decrease in peptic ulcers (Vergara, 2005). Hence, *H.pylori* testing and treatment has been advocated in naïve aspirin or NSAID users prior to treatment initiation and in chronic users with recent ulcer or increased ulcer complication risk (Papatheodoridis *et al.,* 2005).

Although *H.pylori* eradication has decreased PUD incidence rate in the overall population consuming NSAIDs, particularly naïve patients, PPI maintenance has been more effective in PUD prevention (Vergara *et al.,* 2005). Management of *H.pylori* in patients taking COX-2 selective inhibitors can be based upon the same risk assessment as in patients not taking NSAID (Chan *et al.,* 2002).

3.7.12 Genetics and other causes

More than 20% of patients have a family history of duodenal ulcer, compared with only 5 - 10% of control groups. A rare genetic association exists between familial hyperpepsinogenemia type-I (a genetic phenotype leading to enhanced secretion of pepsin) and duodenal ulcer. The high concordance for monozygous twins reared apart, provide data that human genetic factors contribute substantially to determining who will be infected with *H.pylori* and who will ultimately be at risk for the spectrum of gastritis, peptic ulcer disease, and gastric cancer. Other diseases and risk factors associated with PUD are

(1) Gastrinoma (Zollinger-Ellison syndrome [ZES])

(2) C 1- esterase deficiency

(3) Neuhauser's syndrome

(4) Van Allen's amyloidosis

(5) Systemic mastocytosis

(6) Basophilia

(7) Infections - Herpes simplex virus-1 (HSV-1) and cytomegalovirus (CMV)

(8) Chemotherapy - 5-fluorouracil, methotrexate, and cyclophosphamide

(9) Radiation

(10) Crack cocaine

3.8 Management of drug-induced UGI bleeding

3.8.1 Medical management of unstable patient with bleeding ulcer

Stabilisation of the patient with oxygen therapy, infusion of volume expanders and blood transfusion are to be done immediately after securing the airways. Urgent UGI endoscopy is the treatment of choice in the setting of bleeding peptic ulcer for diagnostic and therapeutic reasons. Endoscopy provides an opportunity to visualise the ulcer, to determine the degree of active bleeding, and to attempt hemostasis by direct measures.

Medical management by acid suppression usually serves as an adjunct to direct endoscopic therapy. Reducing gastric acidity is believed to improve hemostasis primarily through the decreased activity of pepsin, which is believed to antagonize the hemostatic process by degrading fibrin clots. Many gastroenterologists assert that intravenous PPI therapy maintains hemostasis more effectively than intravenous H_2RA (Barkun, 2003).

Parenteral PPI is administered after successful endoscopic therapy for ulcers with high-risk signs, such as active bleeding, visible vessels, and adherent clots as an 80 mg bolus followed by a continuous 8-mg/hr. infusion for 72 hours. This treatment is changed to oral PPI therapy after 72 hours if no re-bleeding occurs. Parenteral PPI use before endoscopy is common practice, and evidence from a recent Canadian database (RUGBE) indicates some benefit in decreasing re-bleed rates (Barkun, 2003). Concomitant *H.pylori* infection in the setting of bleeding peptic ulcers should be eradicated, as this lowers the rate of re-bleeding (Kikkawa, 2005).

3.8.2 Medical management of stable patient with NSAID induced ulcer

Discontinuation of NSAIDs is paramount if it is clinically feasible. In general, 6-8 weeks of therapy with a PPI is required for complete healing of NSAID ulcers. Misoprostol use significantly reduced the rate of gastric ulcers both in short-term and long-term NSAID treatment. Treatment of *H.pylori* infection if present is recommended. For patients who must continue with their NSAIDs, PPI maintenance is recommended to prevent recurrences even after eradication of *H.pylori* (Lai, 2002; Lai, 2003). If NSAIDs must be continued, changing to a COX-2 selective inhibitor is an

option. However, use of a traditional NSAID and once-daily PPI is comparable to a selective COX-2 inhibitor with respect to ulcer bleeding in patients with a history of PUD (Chan, 2002).

Concomitant *H.pylori* infection in the setting of bleeding peptic ulcers should be eradicated with lansoprazole 30 mg PO bid or omeprazole 20 mg PO bid, plus amoxicillin 1000 mg PO bid and clarithromycin 500 mg PO bid for 14 days. Lansoprazole 30 mg PO bid or omeprazole 20 mg PO bid, plus metronidazole 500 mg PO bid and clarithromycin 500 mg PO bid for 14 days can also be used. New evidence shows that 7-day treatment is adequate in those patients who have not failed prior attempts at eradication (Gisbert, 2005).

3.8.3 Surgical care

Surgical management of duodenal ulcers is generally reserved for refractory ulcers and bleeding ulcers that fail to respond to medical management.

(i) Endoscopic therapy

Endoscopic therapeutic intervention is indicated for bleeding duodenal ulcers with high-risk signs (e.g., active bleeding, visible vessels, adherent clots). Several tools are available to the endoscopist to achieve hemostasis; these tools include bipolar cautery, use of a heater probe or hemoclips, argon plasma coagulation, and local injection of epinephrine and other agents (Lo, 2006).

(ii) Urgent surgical management

The indications for urgent surgery include the following: (1) failure to achieve hemostasis endoscopically, (2) recurrent bleeding despite endoscopic attempts at achieving hemostasis (many advocate surgery after 2 failed endoscopic attempts), and (3) perforation. In general, 5% of bleeding ulcers eventually require operative management. Most emergent surgical procedures involve simple over-sewing of the ulcer to achieve hemostasis.

(iii) *Elective surgical management*

The indications for elective surgical management (Selective vagotomy, highly selective vagotomy) include the following: (1) refractoriness to medical treatment, (2) intolerance to medications, and (3) noncompliance with medications. With the advent of improved antisecretory therapy and with the discovery of *H.pylori,* elective surgical management of duodenal ulcer has become much less common.

* * *

CHAPTER - 4 MATERIALS AND METHODS

- Materials and methods
- Selection of patients
- Study method
- Study approach

4.1 Materials and methods

Place of study	**:** Department of Internal Medicine, Thanjavur Medical College hospital, Thanjavur
Type of study	: Prospective study
Period of study	: March 2006 to August 2007
Ethical Committee approval	: The present study was approved by the Ethical Committee
Collaborating Department	: Department of Medical Gastro Enterology
Consent	: Informed consent was obtained from the participants

4.2 Selection of patients

Fifty patients satisfying the following inclusion criteria and not having any of the exclusion criteria were taken up for the study.

4.2.1 Inclusion criteria

(1) All adult patients of both sexes who were giving definite history of intake of drugs and subsequently developed vomiting of frank blood or coffee ground coloured vomit and/or passed dark coloured stools were chosen for this study.

(2) Inpatients admitted for other illnesses and who subsequently developed UGI bleeding following prescription with drugs like aspirin, other NSAIDs, steroids, anticoagulants and other gastro toxic drugs were also included.

(3) Standard definitions of hematemesis and malena were used when abstracting data from the clinical records.

4.2.2 Exclusion criteria

The following groups of patients were excluded from this study after detailed history taking, clinical examination and investigations because of the confounding factors which will interfere with the results.

(1) Patients with past history of hematemesis and/or malena

(2) UGI endoscopy finding of other causes of UGI bleeding (e.g. Varices, Mallory weiss syndrome etc.)

(3) Bleeding and clotting disorders

(4) Cirrohosis of liver with portal hypertension

(5) Hematological disorders and

(6) Critically ill patients with life expectancy < 72 hr.

4.3 Study method

4.3.1 History

Patient characteristics like age and sex were noted. Detailed history regarding the UGI bleeding like, number of times of hematemesis, approximate quantity of blood vomited each time, associated with malena or presenting with malena alone and past H/O hematemesis and/or malena were obtained. Symptoms of GI toxicity of the drugs, symptoms of common diseases that can lead to UGI bleeding and symptoms due to blood loss were recorded in the questionnaire.

Detailed history regarding the drug that caused UGI bleeding like

(1) Generic name of the drug

(2) Number of tablets or capsules ingested by the patient

(3) Strength of the drug and duration of drug intake

(4) Nature of the drug like enteric coated (EC) or sustained release (SR) or conventional drug

(5) Whether the drug was prescribed by a qualified medical practitioner or self medicated / OTC

(6) Whether the drug was taken along with a gastroprotective drug like antacid, H_2 receptor blocker or proton pump inhibitor and

(7) Whether the drug was taken on empty stomach, were asked.

Detailed history was asked from the patients regarding the risk factors of drug-induced UGI bleeding.

(1) Known peptic ulcer disease (diagnosed by a physician or a gastroenterologist)
(2) Alcoholism (those who are consuming alcohol at least 100 ml/day regularly for $\geq$ 3 months)
(3) Smoking (those patients who are smoking one or more beedies or cigarettes per day regularly for $\geq$ 3 months)
(4) Stress and serious systemic illnesses of the patients
(5) Concomitant intake of drugs that may cause or aggravate UGI bleeding when taken along with NSAIDs like anticoagulants, steroids, biphosphonates and chemotherapeutic agents were obtained
(6) Past H/O hypertension, diabetes, pulmonary tuberculosis, CAHD, asthma, COPD and other serious systemic illnesses were also noted.

4.3.2 Clinical examination

Routine general and systemic examination of the patients was carried out with the aim of

(1) Assessing the general condition of the patient
(2) Confirmation of UGI bleeding by Ryle's tube aspiration and/or per rectal examination
(3) Assessing severity of blood loss and
(4) Ruling out other common causes of gastrointestinal bleeding like cirrhosis of liver with portal hypertension.

4.3.3 Laboratory investigations

Routine urine and blood investigations to find out diabetes, renal failure, hepatic failure, bleeding and clotting disorders and hematological disorders were carried out.

Blood grouping and typing was done not only for transfusion of blood but also to find out the role of blood group 'O' in drug- induced UGI bleeding. Serological test for *H.pylori* (demonstration of anti- *H.pylori* IgG) was done to find out the association of this bacterium with drug-induced UGI bleeding.

4.3.4 Upper gastrointestinal endoscopy

Endoscopy was done for all the patients after overnight fasting, using PENTAX video endoscopic system **(Figure 4.1)**, to directly visualise the side effects of the drugs on the mucosa of the esophagus, stomach and duodenum, like mucosal hemorrhages, erosions, superficial ulcers and deep ulcers **(Figure 4.2)**.

The number of ulcers, site and location of ulcers, size of ulcers, bleeding or not, healing ulcer or not, clean base of the ulcer or adherent blood clot, oozing of blood from the ulcer base and about visible blood vessel were studied.

Figure 4.1 PENTAX video endoscopic system at Department of Medical Gastro Enterology, Thanjavur Medical College

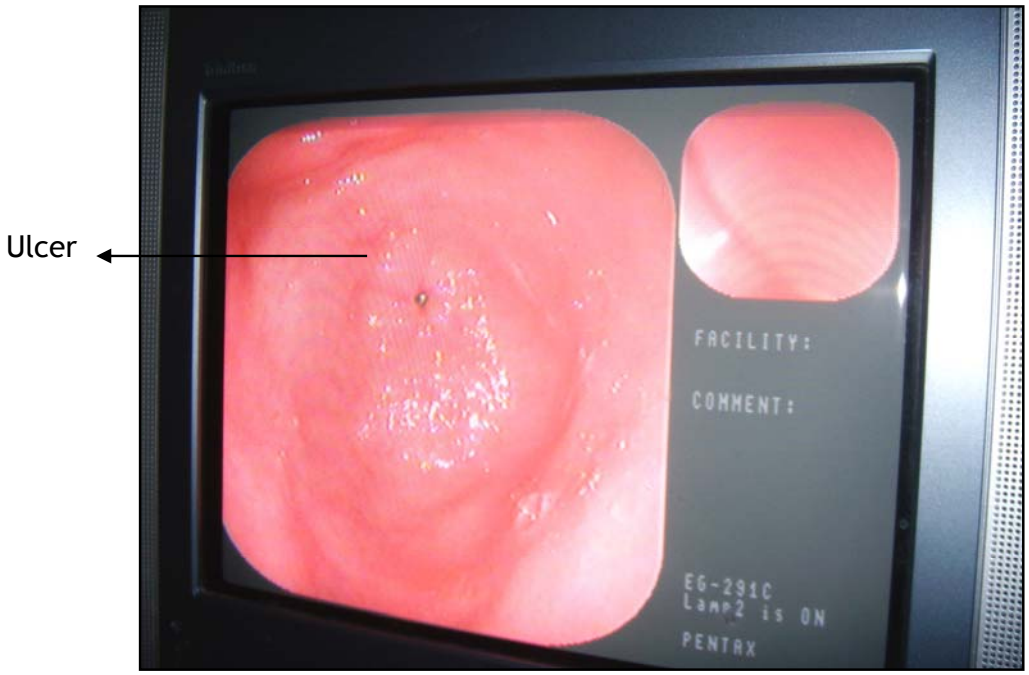

Figure 4.2 Endoscopy showing antral ulcer (done on 17-7-2007)

4.4 Study approach

Number of patients affected, were studied with respect to age group, number of bouts of hematemesis, approximate quantity of total blood loss, causative drug responsible for UGI bleeding, risk factors of GI bleeding, number of individual risk factors in each patients and endoscopic findings in the patients. The prevalence of individual risk factors in those fifty patients and the prevalence of number of risk factors in those fifty patients were studied.

* * *

CHAPTER - 5 RESULTS AND OBSERVATIONS

- Study results and observations

5.1 Study results and observations

After studying the fifty cases, results were arrived from the proforma of all the patients. Prevalence of drug-induced UGI bleeding related to age group and sex were given below in **Table 5.1**. It was found that majority of the patients (48%) were in the age group of 50-64 years.

The number of times of hematemesis the patients had developed and the number of patients affected in each group were given below in **Table 5.2.** It was found that percentage of patients with one episode of hematemesis and two episodes of hematemesis was 36% each. Patients had maximum of five episodes of hematemesis.

Approximate quantities of total blood loss and the number of patients affected in each group were shown in **Table 5.3**. It was observed that majority of patients (54%) were having minor UGI bleeding with < 100 ml of blood loss and three patients had only malena.

The causative drugs for UGI bleeding and the number of patients who took the drugs were shown in **Table 5.4**. From this table it was found that ibuprofen was the causative drug in as high as 19 patients followed by diclofenac in 11 patients and aspirin in 8 patients.

Prevalence of endoscopic findings in the patients, with reference to the site of lesions was given in **Table 5.5**. From this table it was observed that 'lesions in stomach only' was the commonest finding (50%). Endoscopy was normal in 20% of cases while 20% of cases had lesions in both stomach and duodenum.

Prevalence of nature of lesions on endoscopic study (Ulcers and erosions) was given below in **Table 5.6**. It was found that ulcers were more common (64%) than erosions (16%).

The prevalence of risk factors of drug-induced UGI bleeding among the patients was given in **Table 5.7**. It was observed that old age ≥ 50 years was the risk factor with highest prevalence (66%) followed by 'O' blood group (50%).

Prevalence of patients with drug-induced UGI bleeding with respect to number of risk factors was given in **Table 5.8.** It was observed that all the patients (100%) had at least one of the known risk factors and majority of patients (32%) had two risk factors of drug induced UGI bleeding.

Table 5.1 Prevalence of drug-induced UGI bleeding related to age group and sex

S.No.	Age group	Male patients	Female patients	Total	%
1.	Age ≤ 19	0	0	0	0%
2.	Age 20 – 34	6	3	9	18%
3.	Age 35 – 49	5	3	8	16%
4.	Age 50 - 64	16	8	24	48%
5.	Age 65 – 79	4	4	8	16%
6.	Age ≥ 80	1	0	1	2%
7.	Number of patients	32	18	50	100%

Table 5.2 Frequency of hematemesis

S.No.	Number of bouts of Hematemesis	Number of patients
1.	One	18
2.	Two	18
3.	Three	4
4.	Four	5
5.	Five	2

Table 5.3 Approximate quantity of blood loss

S.No.	Quantity of blood loss	Number of patients
1.	< 100 ml	27
2.	100 to 1000 ml	16
3.	> 1000 ml	4
4.	H/O of Malena alone	3

Table 5.4 Causative drugs and number of patients

S.No.	Causative drugs	Number of patients
1.	Aspirin	8
2.	Diclofenac	11
3.	Ibuprofen	19
4.	Indomethacin	4
5.	Mefenamic acid	3
6.	Nimesulide	4
7.	Piroxicam	1

Table 5.5 Prevalence of site of lesions on endoscopic study

S.No	Endoscopic findings	Number of patients (%)
1.	Normal study	10 (20%)
2.	Lesions in esophagus	0 (0%)
3.	Lesions in stomach only	25 (50%)
4.	Lesions in duodenum only	10 (20%)
5.	Lesions in both stomach & duodenum	5 (10%)

Table 5.6 Prevalence of nature of lesions on endoscopic study

S.No	Nature of lesions	Number of patients
1.	Erosions	8 (16%)
2.	Ulcers	32(64%)
3.	Normal endoscopy	10 (20%)

Table 5.7 Prevalence of risk factors of drug-induced UGI bleeding

S.No	Risk factor	Male (%)	Female (%)	Total (%)
1.	Old age $\geq$ 50 yrs	21(42%)	12(24%)	33(66%)
2.	High doses/Chronic drug intake	5 (10%)	0	5(10%)
3.	Self medication / OTC	11 (22%)	7 (14%)	18(36%)
4.	Drug intake without GPA	12 (24%)	8 (16%)	20(40%)
5.	Known PUD	1 (2%)	4 (8%)	5(10%)
6.	Alcoholism	21 (42%)	0	21(42%)
7.	Smoking	15 (30%)	0	15(30%)
8.	Stress & SSI	6 (12%)	0	6(12%)
9.	Drug intake with Steroids	2 (4%)	2 (4%)	4 (8%)
10.	Drug intake with Anticoagulants	2(4%)	0	2 (4%)
11.	'O' Blood group	16 (32%)	9 (18%)	25(50%)
12.	Positive for *H.pylori*	3 (6%)	3 (6%)	6(12%)

Table 5.8 Prevalence of patients with drug-induced UGI bleeding with respect to number of risk factors

S.No.	Number of risk factors	Male Patients (%)	Female Patients (%)	Total (%)
1.	0	0	0	0 (0%)
2.	1	1 (2%)	9 (18%)	10 (20%)
3.	2	11 (22%)	5 (10%)	16 (32%)
4.	3	7 (14%)	2 (4%)	9 (18%)
5.	4	9 (18%)	2 (4%)	11 (22%)
6.	5	2 (4%)	0 (0%)	2 (4%)
7.	6	0 (0%)	1 (2%)	1 (2%)
8.	7	1 (2%)	0 (0%)	1 (2%)

Sex distribution among the fifty patients was shown in **Figure 5.1**. It was observed that male patients were more commonly affected than female patients.

Age group distribution was shown in **Figure 5.2.** From the figure It was observed that majority of patients were in the age group of 50-64.

Frequency of hematemesis among the patients was shown in **Figure 5.3.** It was found that majority of patients had only one or two episodes of hematemesis indicating that NSAIDs-induced ulcers heal rapidly once the offending drug was stopped.

Prevalence of causative drugs was given in **Figure 5.4** and it was found that the most commonly prescribed drugs ibuprofen, diclofenac and aspirin were responsible for majority of the cases.

Number of prescribed patients who developed UGI bleeding and the number of self medicated developing UGI bleeding was shown in **Figure 5.5** and it was observed that self medication was also an important risk factor of drug- induced UGI bleeding.

Prevalence of site of lesions on endoscopic study was given in **Figure 5.6**. It was observed from the figure that ten patients were having normal endoscopic study, twenty five patients were having lesions in stomach only, ten patients were having lesions in duodenum only and five were having lesions in both stomach and duodenum. None of the patients studied, had lesions in the esophagus. The ten patients who had normal endoscopic study were done UGI endoscopy three to five days later.

Prevalence of nature of lesions on endoscopic study was given in **Figure 5.7.** It was found that ulcers were more common than erosions.

Prevalence of each individual risk factor in patients with drug-induced UGI bleeding was shown in **Figure 5.8.** It was observed that old age $\geq$ 50 years, 'O' blood group, not taking gastroprotective agents along with NSAIDs, self medication and getting NSAIDs over the counter, taking NSAIDs despite knowing the peptic ulcer problem and H.pylori infection were the major risk factors present in female patients while the male patients also had other major risk factors like alcoholism, smoking and chronic drug intake.

Prevalence of patients with drug-induced UGI bleeding with respect to number of risk factors was shown in **Figure 5.9.** It was found that higher the number of risk factors the lower the number of female patients and that majority of male patients were having two to four risk factors while the majority of female patients were having one or two risk factors.

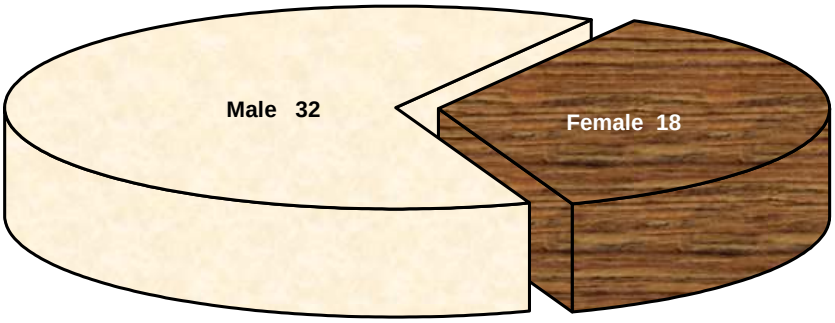

Figure 5.1 Sex distribution

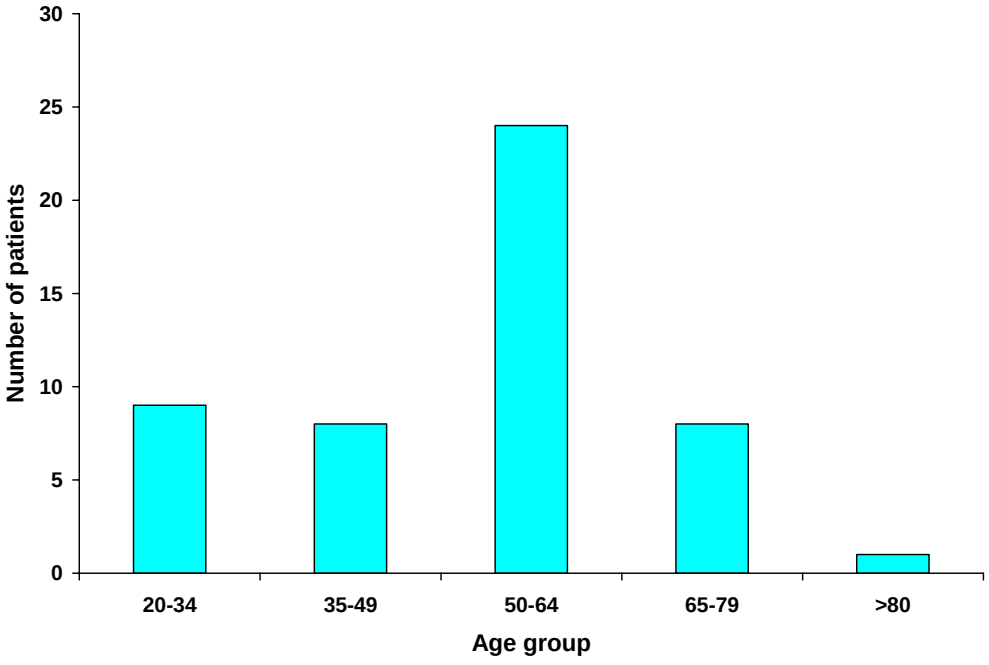

Figure 5.2 Age group distribution

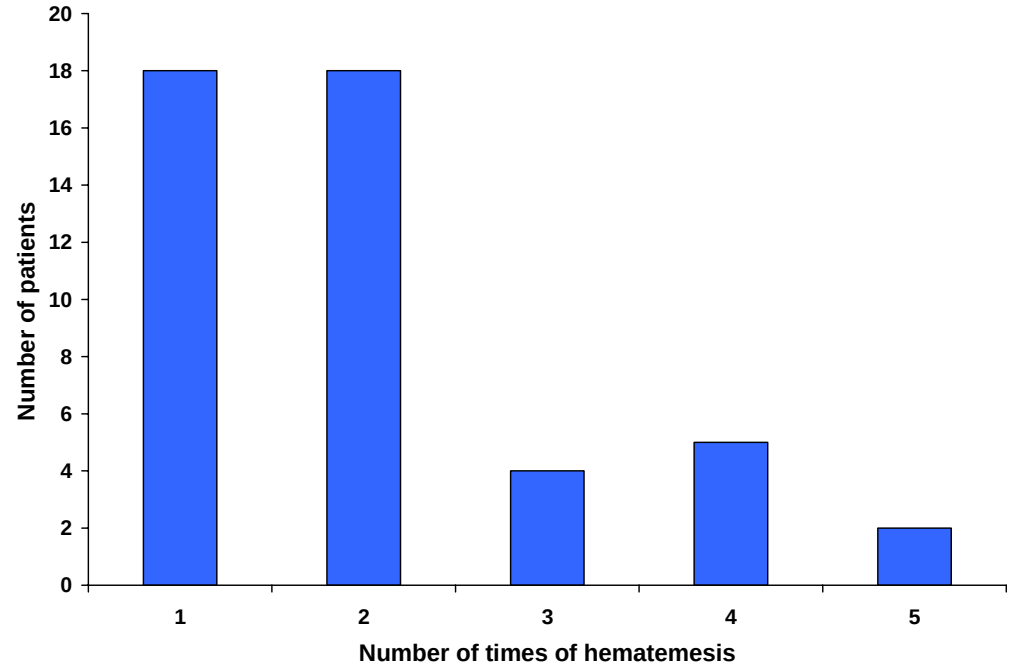

Figure 5.3 Frequency of hematemesis

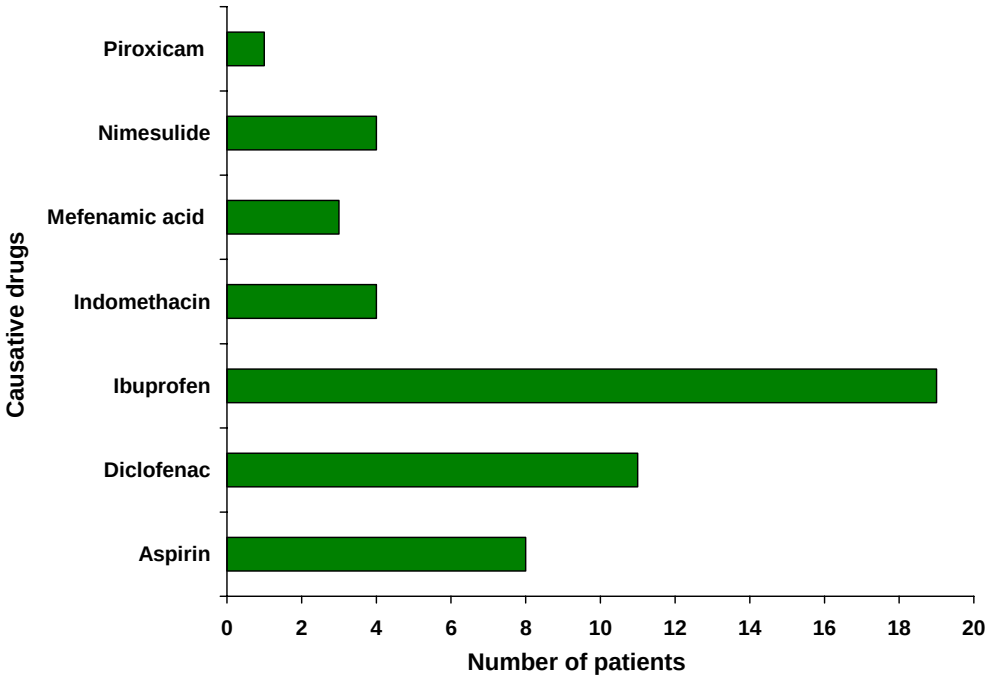

Figure 5.4 Prevalence of causative drugs

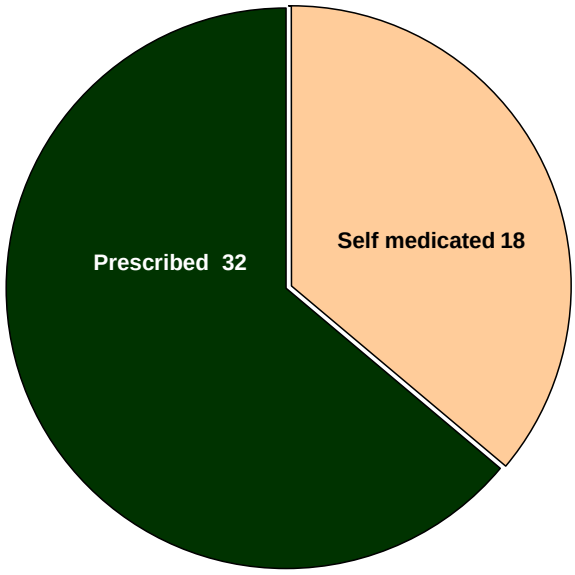

Figure 5.5 Prescription vs. Self medication / OTC

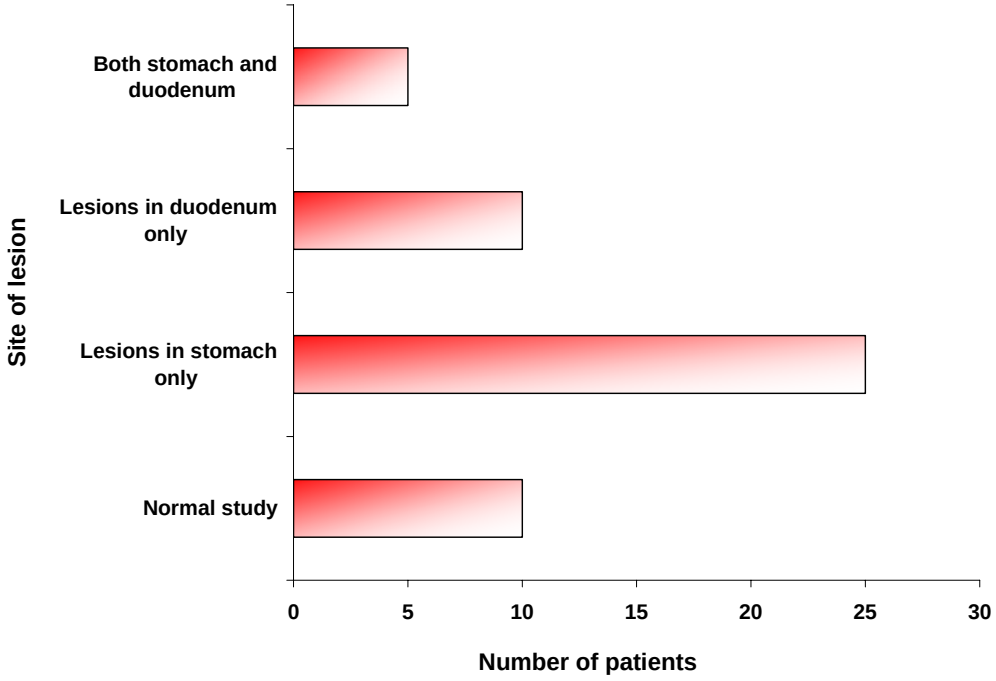

Figure 5.6 Prevalence of site of lesions on endoscopic study

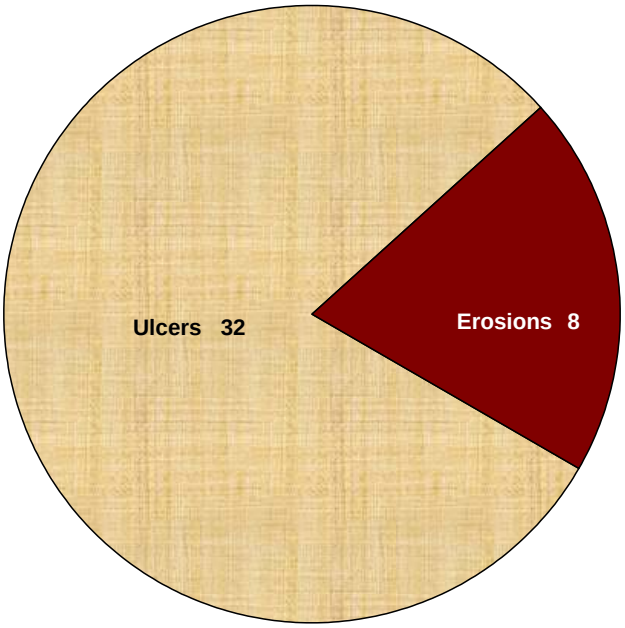

Figure 5.7 Prevalence of nature of lesions on endoscopic study

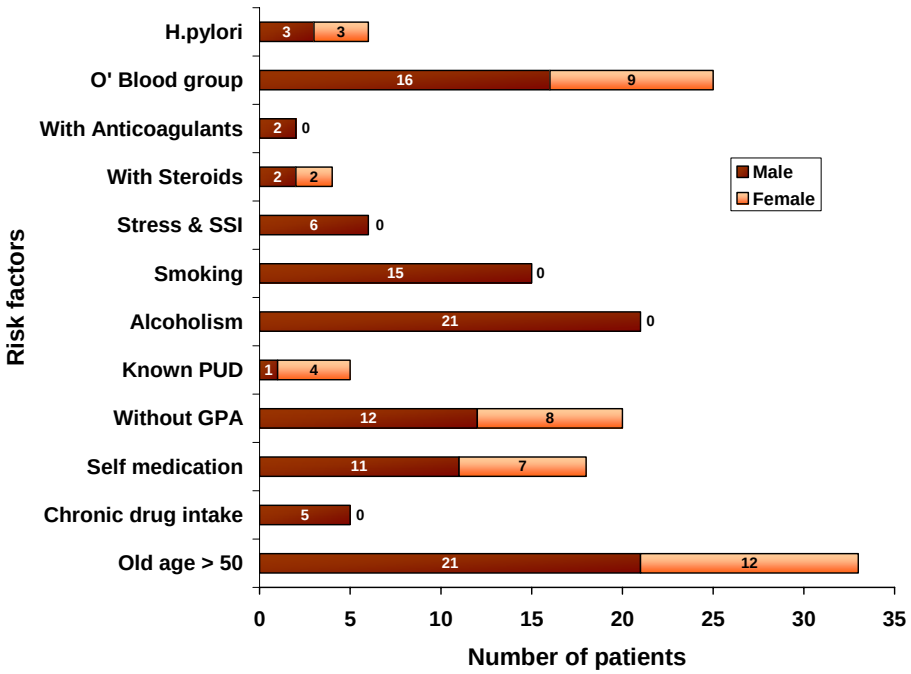

Figure 5.8 Prevalence of individual risk factors among the patients

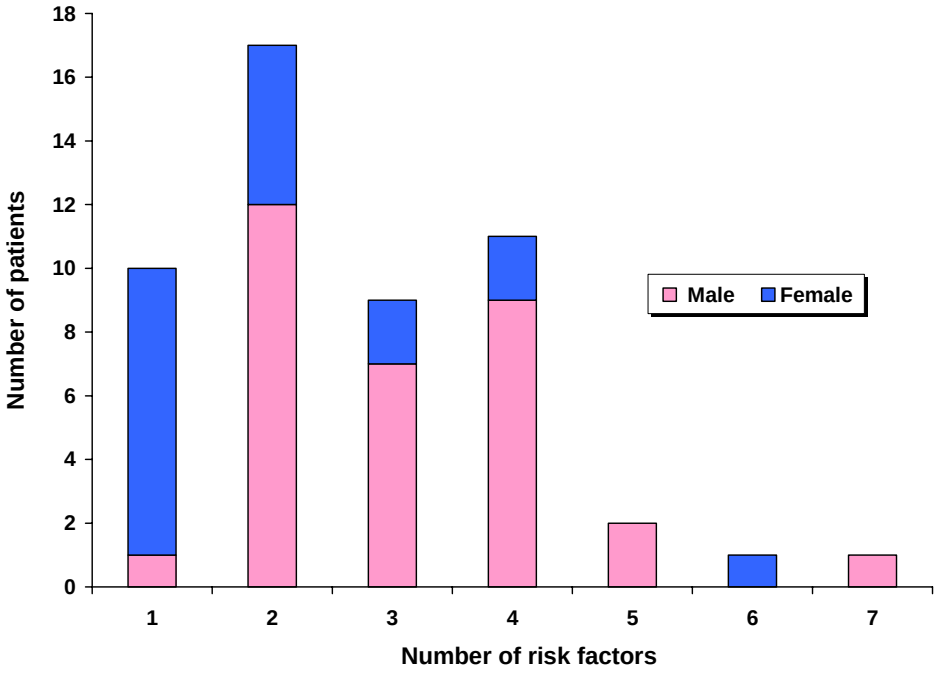

Figure 5.9 Prevalence of patients with drug-induced UGI bleeding with respect to number of risk factors

* * *

CHAPTER - 6 DISCUSSION

- Discussion

6.1 Discussion

6.1.1 Sex

Out of the fifty patients studied, thirty two were male patients which gave the male: female ratio of 1.77:1. In a Scandinavian study, it was found that the incidence of drug induced UGI bleeding was twice as high among men as among women (Oliver *et al.,* 1997). In a Sri Lankan study it was discussed that the incidence of drug induced UGI bleeding among male and female patients was in the ratio of 1: 2.125 (Satarasinghe and Jayamaha, 2000).

6.1.2 Age

The percentage of number of patients in the age group of equal to or above 50 yrs of age was 66%, comprising 2/3 of all the patients. In this present study, it was found that the elderly patients $\geq$ 50 years of age were frequently prescribed NSAIDs and aspirin for their orthopedic and cardiac problems and the relative risk was 2.0 times higher than the others.

In the early study by Griffin *et al.,* (1991) the relative risk for elderly patients with age group of $\geq$ 65 years was 3.8 times than the others.

A Sri Lankan study found that majority of the patients were in the middle age or elderly group, prone to high risk of NSAID induced gastric injury (Satarasinghe and Jayamaha, 2000).

In an Indian study by Vikas *et al.,* in 2003, seventy percent of the patients admitted with drug induced UGI bleeding were $\geq$ 50 years of age. The lesser average life span of Indian population, early onset of arthralgia, arthritis, low backache, sciatica, spondyloses and coronary artery heart diseases in our population may be the reasons for the higher prevalence of drug induced UGI bleeding at an earlier age compared to the western population (Vikas *et al.,* 2003).

6.1.3 Severity of hematemesis

Percentage of patients with one or two episodes of hematemesis was 72% and 54% of the patients admitted with drug-induced UGI bleeding were having minor UGI bleeding (< 100 ml). Only 8% of the patients had severe UGI bleeding (> 1000 ml) in the present study and majority of those patients were found to have four or more risk factors. None of the patients studied, died during the hospital stay.

NSAID-induced peptic ulcers usually heal very rapidly once the offending drug is stopped. Mortality is high in patients, already known to have peptic ulcer disease, who are taking NSAIDs in high doses for prolonged period and in patients who are concomitantly taking steroids and anticoagulants (Loren, 2001).

6.1.4 Causative drugs

Ibuprofen was responsible for the majority of cases of drug-induced UGI bleeding in the fifty patients studied accounting for 38% and the doses fell within safe limits. Diclofenac was the second fashionable drug (22%), and both drugs had already been proved to be safer than the other nonselective NSAIDs in the previous studies. Aspirin was hardly ever used in the management of chronic arthritic conditions and was mainly prescribed for cardiac patients in low doses (150 mgs). Ibuprofen and diclofenac are preferred by many practitioners because of their less GI toxicity compared to other nonselective NSAIDs. These three drugs were responsible for 76% of all the cases of drug-induced UGI bleeding and tell us the fact that all NSAIDs including aspirin even in safer doses can cause serious GI complications. In the present study all the patients were prescribed or self medicated within the safer limit of doses. Aspirin was the only drug found to have been taken regularly for prolonged period, in this study.

Although the bleeding risk increases in proportion to NSAID dose, any doses of NSAIDs (including low-dose aspirin taken for cardiovascular prophylaxis) may cause bleeding (Dalton *et al.,* 2003).

It was found in the study that the NSAID nimesulide which was banned few years back was still prescribed in 6% of cases and it was available over the counter in 2% of cases and nimesulide was responsible for UGI bleeding in 8% of the patients studied. Among the eighteen patients who got the drugs over the counter, many chose ibuprofen (9 patients) or diclofenac (8 patients). None of the patients in this study took COX-2 selective inhibitor.

6.1.5 High doses / Chronic drug intake

In the present study, only 10% of the patients were taking drugs for longer period $\geq$ 3 months. All of them were prescribed patients taking aspirin for their cardiac illnesses. Other NSAIDs were not taken by the patients regularly for prolonged period. All the patients studied, were prescribed or self medicated within the safer limit of doses.

The risk of bleeding increases with incremental doses of aspirin and most NSAIDs especially with ibuprofen, diclofenac and piroxicam (Singh, 1999). Risk of deaths due to NSAIDs induced severe GI bleeding, is high in patients taking higher doses of NSAIDs for years (Laine 1999).

6.1.6 Self medication / OTC

A large study involving 421 patients admitted to a hospital in United Kingdom with upper gastrointestinal haemorrhage, who took NSAIDs, revealed that non-prescription drug use was an important cause of bleed in 30% of patients (Hawkey *et al.,* 1998; Graham *et al.,* 2002).

In the present study, self medication was observed in 36% of patients. Seven of the eighteen female patients studied (38.89%), took NSAIDs on their own, while eleven of the thirty two male patients (34.38%) were found self medicated. Ibuprofen (50%) and diclofenac (44.44) were the drugs preferred by seventeen of the eighteen patients who took the drug over the counter.

6.1.7 Drug intake without Gastroprotective agents

Gastroprotective agents are often co-prescribed with NSAIDs, with the aim to reduce the associated GI adverse effects. Co-prescribing rates range from 17 to 34% in the literature (Rogind *et al.,* 1997). The most commonly used GPAs include proton pump inhibitors (PPIs), H_2 receptor antagonists (H_2RA) and misoprostol. Parenteral PPIs are the most efficacious of all the gastroprotective drugs in patients with NSAIDs-induced UGI bleeding (Loren 2001).

In the current study, 40% of the patients didn't take a gastroprotective drug along with NSAID. Others took either antacids (34%) or H_2 receptor antagonists (26%).

6.1.8 Known PUD

The use of any NSAID, including low-dose (i.e., ≤ 150 mg/day) aspirin, was associated with an increased risk (18 folds higher risk when compared to normal population) of GI bleeding in a patient with known peptic ulcer disease and NSAIDs including aspirin should never be taken on an empty stomach (Lanas *et al.,* 2000).

In the present study, one male patient and four female patients despite knowing about previous episode of peptic ulcer disease, took NSAID and developed UGI bleeding. Three of those female patients took the NSAIDs without prescription. Twenty percent of the total number of patients studied gave history of NSAID intake on empty stomach. These findings suggest that physicians must always enquire patients about the past history

of PUD before prescribing any NSAID and that they should educate the patients about the adverse effects of the drugs they are prescribing.

6.1.9 Alcoholism

Ethanol is known to cause gastric mucosal irritation and nonspecific gastritis. Nonsteroidal anti-inflammatory drugs (NSAIDs) and alcohol consumption increase the risk for major upper gastrointestinal bleeding. Kaufman and associates studied the relationship between aspirin and ibuprofen in upper GI bleeding with various levels of alcohol consumption. As the quantity of alcohol consumption increased, the relative risk of upper GI bleeding also increased, up to a relative risk of 2.8 in heavy alcohol consumers (Kaufman *et al.,* 1999).

The use of aspirin increased the risk at all levels of alcohol consumption. With regular use, the relative risk for upper GI bleeding in alcohol consumers taking more than 325 mg of aspirin per day was 7.0. Regular use of ibuprofen was also found to increase the relative risk for upper GI bleeding in alcohol consumers (Kaufman, et al., 1996).

In the present study alcoholism was found in 42% of patients with UGI bleeding all of them were males. Also, alcoholism emerged as the third most important independent risk factor for UGI bleeding in this study.

6.1.10 Smoking

Smoking is found to be associated with a threefold elevation in the risk of UGI bleeding in patients taking NSAIDs compared with no smoking (Peura, 2004). Ulcer healing with H_2 receptor antagonists is significantly delayed in smokers compared to non smokers. Also the relapse rate of duodenal ulcer is higher in smokers compared with non smokers (Korman *et al*., 1981).

One study reported that after ulcers healed, about half of nonsmokers experienced a relapse of their ulcer disease after one year, but that all heavy smokers relapsed after three months. However, smoking in the setting of *H.pylori* infection may increase the risk of relapse of PUD (Sonnenberg, 1981).

In the current study, 30% of the patients were having the risk factor of smoking and all of them were males. Only one smoker in this study had *H.pylori* infection and known peptic ulcer disease.

6.1.11 Stress and Serious systemic illnesses

About 75 – 100% of ICU patients will have endoscopic lesions within 24 hours, but only a small percentage develop stress related gastric bleeding (Goldin and Peura, 1996). In the ICU patients with UGI bleeding, 23.95% had respiratory failure, 19.79% had CNS problems and 16.79% had cardiovascular dysfunction, 12.27% had Sepsis (Manucherhr, 2007).

In the present study 12% of patients were having serious systemic illnesses. They had been suffering from coronary artery heart diseases (4 patients) or COPD with respiratory failure (2 patients) and all of them were male patients.

6.1.12 Concomitant use of Steroids

Glucocorticoids lead to atrophy of all epithelial tissues including gastro intestinal mucosa and their role in ulcerogenesis is relatively small. Haemorrhage in steroid users is related to duration of therapy and dose (Messer *et al.,* 1983; Fadul *et al.,* 1988). Steroids when combined with low doses of aspirin or non selective NSAIDs or COX-2 selective inhibitors increase the chances of UGI bleeding four folds (Fabrice *et al.,* 1998).

In the present study, concomitant intake of steroids contributed as a risk factor in eight percent of cases of NSAIDs induced bleeding. The patients who took steroids along with NSAIDs were taking steroids for more than three months in optimal doses for their respiratory problems.

6.1.13 Concomitant use of Anticoagulants

Aspirin, in low doses (150 mg) was prescribed along with injection Heparin in 4% of patients studied, for CAHD for four days and was able to cause moderate UGI bleeding (100 ml to 1000 ml) in them. This is one of the frequently used combinations in CAHD patients (in ICCU and general ward inpatients) and this study makes us alert about the increased risk of aspirin induced UGI bleeding when taken along with anticoagulant.

Anticoagulants do not cause GI bleeding per se, but they can unmask or aggravate hemorrhage from preexisting lesions (Dalton *et al.,* 2003).

6.1.14 'O' Blood group

Patients who do not secrete ABO antigens in their saliva and gastric juice are known to be at higher risk of UGI bleeding. In an earlier study 52.8% of patients with bleeding duodenal ulcers were found to have 'O' blood group (Boren *et al.,* 1993). Study by Kuyvenhoven *et al.,* in 1999 didn't find any potentiation of 'O' blood group on NSAIDs induced ulceration.

In the present study half of all those fifty patients studied were found to have 'O' blood group. It had emerged as the second most important independent risk factor.

6.1.15 H.pylori

So far, both positive (Aalykke *et al.,* 1999) and negative (Santolaria *et al.,* 1999; Stack *et al.,* 2002; Okan *et al.,* 2003) interactions have been reported between *H.pylori* infection and the use of NSAIDs, while other reports have suggested that *H.pylori* and NSAIDs are independent risk factors in the etiology of UGI bleeding (Cullen *et al.,* 1997; Pilotto *et al.,* 1997; Labenz *et al.,* 1999; Wu *et al.,* 1999; Hunang *et al.,* 2002).

Most evidence now supports the assertion that *H.pylori* and NSAIDs are synergistic with respect to the development of PUD. Eradication of *H.pylori* in the setting of chronic NSAID use is associated with a decreased risk of ulcer bleeding (Lai, 2002).

In the current study, the percentage of patients with drug-induced UGI bleeding, affected with *H.pylori* was only 12%.

6.1.16 Relationship between OTC and GPA

Number of patients who were self medicated was eighteen, while the number of patients who didn't take a gastroprotective agent was twenty. Among the eighteen self medicated patients there were two male patients and one female patient who took gastroprotective drugs along with NSAID. It was found that majority (15) of those taking drugs on their own (18) didn't take a gastroprotective agent.

There appears to be a direct relationship between self medication and not taking a gastroprotective drug along with NSAIDs (Lai, 2002).

6.1.17 Endoscopic findings

In the present study, endoscopy was normal in 20% of cases. They had undergone delayed UGI endoscopy by three to five days and they had only minor UGI bleeding. On follow up they didn't develop further bleed.

NSAID-induced peptic ulcers usually heal very rapidly once the offending drug is stopped (Loren, 2001).

No one had findings in esophagus. Gastric lesions alone were found in 50% of cases, duodenal lesions alone were found in 20% of cases and in 10% of cases, findings were seen in both stomach and duodenum. Erosions in stomach were seen in 10% of patients while ulcers in stomach were seen in

40% of patients. Similarly, erosions in duodenum were seen in 4% of patients while duodenal ulcers were found in 16% of cases. Among the patients with lesions in both stomach and duodenum, erosions were seen in 2% of patients and ulcers were found in 8% of cases. Hence, ulcers were found to be more common (64%) than erosions (16%).

In an Indian study, incidence of new ulcer cases following NSAID intake, ranges from 10% to 40% for gastric ulcers and 5% - 15% for duodenal ulcers (Simon *et al.,* 1999).

Studies have demonstrated increased intestinal permeability with SR and EC formulations of all NSAIDs but not with conventional release tablets and lower GIT bleeding are also more common with them (Choi *et al.,* 1995).

In the present study only one female patient was prescribed 'sustained release' tablet diclofenac 100 mg, and on endoscopy she was found to have lesions in both stomach and duodenum.

6.1.18 Prevalence of number of risk factors

Of the twelve total numbers of risk factors studied, patients had number of risk factors ranging from one to seven and no one was without a risk factor. Eighty percent of the patients had two or more risk factors of drug-induced UGI bleeding. Majority (28 out of 32) of the male patients had two to four risk factors and majority (14 out of 18) of the female patients had one or two risk factors only.

* * *

CHAPTER – 7 CONCLUSION

- Conclusion

7.1 Conclusion

The present study on drug-induced UGI bleeding concludes that

(1) Non-steroidal anti-inflammatory drugs were the causative drugs for UGI bleeding in all the fifty cases studied.

(2) Among the NSAIDs, the prevalence of causative drugs was as follows: Ibuprofen was the causative drug in 38% of cases, diclofenac in 28%, aspirin in 16% and other non selective NSAIDs in 18% of cases.

(3) In endoscopic study, 'gastric lesions only' was found in 50% (highest percentage); next to that 'duodenal lesions only' in 20% and both gastric and duodenal lesions in 10%. Endoscopy was normal in 20%.

(4) Regarding the nature of lesions, ulcers were more common (64%) than erosions (16%).

(5) All the fifty cases had at least one known risk factor and majority (80%) had more than one risk factors of drug induced UGI bleeding.

(6) The prevalence of risk factors was as follows [1] Old age $\geq$ 50 years of age - 66% [2] 'O' Blood group – 50% [3] Alcoholism – 42% [4] Not using Gastroprotective agents – 40% [5] Self medication / OTC drugs – 36% [6] Smoking – 30% [7] Stress and Serious systemic illnesses – 12% [8] Helicobacter pylori – 12% [9] Known Peptic ulcer disease – 10% [10] High doses / Chronic drug intake – 10% [11] Concomitant use of Steroids – 8% [12] Concomitant use of Anticoagulants – 4%.

REFERENCES

A

Aalykke, C., Lauritsen, J.M., Hallas, J., Reinholdt, S., Krogfelt, K. and Lauritsen, K. (1999) Helicobacter pylori and risk of ulcer bleeding among users of nonsteroidal anti-nflammatory drugs: a case-control study. *Gastroenterology, v.*116, pp. 1305 -1309.

Aihie, A.P., Halpern, S.M., Streete, P.J. and Crome, P. (1994) Slow release aspirin in the elderly. *Journal of the royal society of medicine*, v.87, pp. 183 - 186.

Al Mofleh, I.A., Alhaider, A.A., Mossa, J.S., Al-Sohaibani, M.O., Qureshi, S. and Rafatullah, S. (2005) Pharmacological studies on 'Clove' Eugenia caryophyllata. *PHCOG Magazine,* v.1, pp. 105 – 109.

Al Mofleh, I.A., Al Haider, A.A., Mossa, J.S., Al-Sohaibani, M.O., Rafatullah, S. and Qureshi, S. (2005) Inhibition of gastric mucosal damage by Piper Nigrum (Black pepper) pretreatment in Wistar Albino Rats. *PHCOG Magazine*, v.1, pp. 64 - 68.

Al Mofleh, I.A., Alhaider, A.A., Mossa, J.S., Al-Sohaibani, M.O., Rafatullah, S. and Qureshi, S. (2006) Protection of gastric mucosal damage by *Coriandrum sativum* L. Pretreatment in Wistar albino rats. *Environmental Toxicology and Pharmacology,* v.22, pp. 64 - 69.

Andrade, S.E., Gurwitz, J.H. and Fish, L.S. (1999) The effect of an Rx-to-OTC switch on medication prescribing patterns and utilization of physician services: the case of H_2-receptor antagonists. *Medical Care*, v.37, pp. 424 - 430.

Arsura, E.D. (1990) Corticosteroid-associated perforation of colonic diverticula. *Archives of Internal Medicine,* v.150, pp. 1337 - 1338.

B

Balint, J. A., Cooper, G. W., Price, E. C. V., Pulvertaft, C. N., and Swynnerton, B. F. A. (1957). *Lancet*, 2, 551.

Bardou, M., Toubouti, Y. and Benhaberou-Brun, D. (2003) High dose proton pump inhibition decreases both re-bleeding and mortality in high risk patients with acute peptic ulcer bleeding: A series of meta-analyses. *Gastroenterology*, v.123, pp. 675 - 680.

Barkun, A., Bardou, M. and Marshall, J.K. (2003) Consensus recommendations for managing patients with nonvariceal upper gastrointestinal bleeding. *Annals of Internal Medicine,* v.139, pp. 843 – 857.

Belsey, Current Medical Research and Opinion, Posted 08/12/2003.

Bjarnason, I., Zanelli, G. and Smith, T. (1987) NSAID induced intestinal inflammation in human. *Lancet*, v.2, pp. 711 - 714.

Bodner, B., Harrington, M.E. and Kim, U. (1990) A multifactorial analysis of mortality and morbidity in perforated peptic ulcer disease. *Surgical Gynecol Obstet.,* v.171, pp. 315 - 320.

Bombardier, C., Laine, L., Reicin, A., Shapiro, D., Burgos-Vargas, R., Davis, B., Day, R., Ferraz, M.B., Hawkey, C.J., Hochberg, M.C., Kvien, T.K. and Schnitzer, T.J. (2000) Comparison of upper intestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *New England journal of medicine,* v.343, pp. 1520 – 1528.

Borelli, F. and Izzo, A.A. (2000) The plant kingdom as a source of anti-ulcer remedies. *Phytotherapy Research*., v.14, pp. 581 - 591.

Boren, T., Falk, P., Roth, K.A., Larson, G. and Nomark, S. (1993) Attachment of *Helicobacter pylori* to human gastric epithelium mediated by blood group antigens. *Science*, v.262, pp. 1892 - 1895.

Brett, S. (2005) Science review: the use of proton pump inhibitors for gastric acid suppression in critical illness. *Critical Care Medicine, v.*9, pp. 45 - 50.

Brown, T.J., Hooper, L. Elliott, R.A. Payne, K. Webb, R., Roberts, C. Rostom, A. and Symmons, D. (2006) *Health Technology Assessment* , v.10, pp. 38.

Brzozowski, T., Konturek, P.C., Sliwowski, Z., Kwiecien, S., Drozdowicz, D. and Pawlik, M. (2006) Interaction of nonsteroidal anti-inflammatory drugs (NSAID) with Helicobacter pylori in the stomach of humans and experimental animals. *Journal of Physiology and Pharmacology,* v.57, pp. 67 - 79.

C

Cameron, J.L. (1995) ed: Current Surgical Therapy. 5th ed. St. Louis, Mo: Mosby-Year Book.

Carbaza, A., Carbre, F. and Rotten, E. (1996) Stereo-selective inhibition of cyclooxygenase by chiral NSAIDs. *Journal of clinical pharmacology*, pp. 505 - 512.

Carlson, J., Notis, W.M. and Corris, E.S. (1990) Colonic ulceration and bleeding during diclofenac therapy (letter). *New England journal of medicine*, *v* .323, pp. 135 - 138.

Carson, J.L., Strom, B.L., Soper, K.A., West, S.L. and Morse, M.L. (1987) The association of non-steroidal anti-inflammatory drugs with upper gastro intestinal tract bleeding. *Archives of internal Medicine,* v.147, pp. 85 - 88.

Chan, K.H., Mann, K.S., Ng, T.H. and Fan, Y.W. (1992) Unusual gastrointestinal complications in neurosurgery. *British Journal of neurosurgery, v.*6, pp. 21 - 26.

Chan, F.K., Hung, L.C., Suen, B.Y., Wu, J.C., Lee, K.C., Leung, V.K., Hui, A.J., To, K.F., Leung, W.K., Wong, V.W., Chung, S.C. and Sung, J.J. (2002) Celecoxib versus diclofenac and omeprazole in reducing the risk of recurrent ulcer bleeding in patients with arthritis. *New England journal of medicine*, v.347, pp. 2104 - 2110.

Chan, F.K., To, K.F., Wu, J.C., Yung, M.Y., Leung, W.K. and Kwok, T. (2002) Eradication of Helicobacter pylori and risk of peptic ulcer in patients starting long-term treatment with non-steroidal anti-inflammatory drugs: A randomized trial. *Lancet, v.*359, pp. 9 - 13.

Charwizi, I., Ovwa, A. and Zinkin, H. (1985) Ibuprofen and benign cecal ulcer. *Journal of Rheumtology, v.*12, pp. 188 - 189.

Choi, V.M.I., Coates, J.E., Chooi, J., Thomson, A.B.R. and Russell, A.S. (1995) Small bowel permeability - a variable effect of NSAIDs. *Clinical and investigative medicine-medecine clinique et experimentale*, v.18, pp. 357 - 361.

Cook, D.J., Witt, L.G., Cook, R.J. and Guyatt, G.H. (1991) Stress ulcer prophylaxis in the critically ill: a meta-analysis. *American Journal of Medicine, v.*91, pp. 519 – 527.

Corder, A. and Steroids, O. (1987) non-steroidal anti-inflammatory drugs, and serious septic complications of diverticular disease. *British Medical journal*, v.295, pp. 1238 - 1242.

Corson, J.D., Williamson, R.C.N., (2001) eds: Surgery. London, UK: Mosby-Year Book.

Cryer, B. and Feldman, M. (1999) Effects of very low dose daily, long-term aspirin therapy on gastric, duodenal, and rectal prostaglandin levels and on mucosal injury in healthy humans. *Gastroenterology,* v.117, pp. 17 – 25.

Cullen, D.J.E., Hawkey, G.M., Greenwood, D.C., Humphreys, H., Shepherd, V., Logan, R.F.A. and Hawkey, C.J. (1997) Peptic ulcer bleeding in the elderly: relative roles of Helicobacter pylori and non-steroidal anti-inflammatory drugs. *Gut,* v.41, pp. 459 – 462.

D

Dajani, A., Dham, R., El-Sahhar, M., Subeih, S., El Sheikh, S. and Mansour, A. (2006) Importance of *Helicobacter pylori* eradication for maintenance of remission of drug associated peptic ulcer disease. *Saudi Journal of Gastroenterology,* v.12, pp. 16 - 20.

Dalton, S.O., Johansen, C. and Mellemkjaer, L. (2003) Use of selective serotonin reuptake inhibitors and risk of upper gastrointestinal tract bleeding: a population-based cohort study. *Archive of Internal Medicine,* v.163, pp. 59 – 63.

Davies, N.M. and Jamali, F. (1997) Influence of dosage from on the gastroenteropathy of lubiprofen in the rat: Evidence of Shift in the toxicity site. *Pharmaceutical research,* v.14, pp. 1597 – 1600.

Davies, N.M., Seth, A.G. and Appley, E. (1997) No-naproxan vs. naproxan: ulcerogenic, analgesic and anti-inflammatory effects. *Alimentary pharmacology and therapeutics*, v.11, pp. 69 - 79.

Deborah, C., Daren, H., Lauren, G., Richard, C., John, M. and Joe, P. (1999) Risk factors for clinically important upper gastrointestinal bleeding in patients requiring mechanical bleeding ventilation, *Critical Care Medicine*, v.27, pp. 12.

Deborah, J. C., Lauren, E. G., Stephen, D. W., Gordon, H. G., Maureen, O. M., Daren, K. H., Ann, K., Michael, T. and for the Canadian Critical Care Trials Group (2001) The attributable mortality and length of intensive care unit stay of clinically important gastrointestinal bleeding in critically ill patients, *Critical Care medicine*, v.5, pp. 368 - 375.

Dequeker, J., Hawkey, C., Kahan, A., Steinbruck, K., Alegre, C. and Baumelou, E. (1998) Improvement in gastrointestinal tolerability of the selective cyclooxygenase (COX) - 2 inhibitor, meloxicam, compared with piroxicam: results of the Safety and Efficacy Large-scale Evaluation of COX inhibiting Therapies (SELECT) trial in osteoarthritis. *British Journal of Rheumatology, v.*37, pp. 946 - 951.

Dhikav, V. (2001) Aspirin misconceptions. *Drugs News and Views*, v.6, pp. 64 - 65.

Dhikav, V., Sindhu, S. and Anand, K.S. (2002) Newer non-steroidal anti-inflammatory drugs: A review of their therapeutic potential and adverse drug reactions. *Journal of investigational allergology and clinical immunology,* v.3, pp. 332 - 338.

Doomra, R. and Gupta, S.K. (2001) Intensive adverse drug reaction monitoring in various specialty clinics of a Tertiary Care Hospital in North India. *Intern J Med Toxicol.,* v. 4, pp. 1 - 4.

E

Emery, P., Zeidler, H., Kvien, T.K., Guslandi, M., Naudin, R., Stead, H., Verburg, K.M., Isakson, P.C., Hubbard, R.C. and Geis, S.G. (1999) Celecoxib versus diclofenac in long-term management of rheumatoid arthritis: randomized double-blind comparison. *Lancet*, v.354, pp. 2106 – 2111.

Erin, D. and Rhonda S. R. (2006) Preventing Stress Related Mucosal Disease in the Intensive Care Unit. *Journal of advanced nursing, v.*8.

Experimental Biology and Medicine (1987). Proceedings of symposium, v.185, pp. 493 – 497.

F

Fabrice, M., Xavier, C., Bertrand, W., Zhou, B. and Jean, P.C. (1998) Diffuse Peritonitis in Steroid-Treated Patients, *Digestive Surgery,* v.15, pp. 247 – 251.

Fadul, C.E., Lemann, W., Thaler, H.T. and Posner, J.B. (1988) Perforation of the gastrointestinal tract in patients receiving steroids for neurologic disease. *Neurology,* v.38, pp. 348 - 352.

Fdes, J.F., Miller, S.R., Spitz, P.W., Williams, C.A., Hubert, H.B. and Bloch, D.A. (1989) Towards an epidemiology of gastropathy associated with Non-steroidal anti-inflammatory drug use. *Gastroenterology,* v.96, pp. 647 - 655.

Ford, A.C., Delaney, B.C. and Forman, D. (2006) Eradication therapy for peptic ulcer disease in Helicobacter pylori positive patients. *Cochrane Database Syst Rev*.

G

Gibson, G.R., Whatacre, E.B. and Ricotti, C.A. (1992) Colitis induced by NSAIDs. Archives of internal medicine, v.*52*, pp. 632 – 635.

Giraud, M.N., Motta, C. and Lichtenberger, L.M. (1997) Effect of aspirin (ASA) on the dynamic properties of gastric surface-active phospholipids. *Gastroenterology,* v.112, pp. 127 - 129.

Giruad, M.N. and Sandujask, F. (1997) The effect of omeprazole on the bioavailability of unmodified and phospholid complexed aspirin in rats. *Alimentary pharmacology and therapeutics,* v.11, pp. 899 - 906.

Gisbert, J.P. and Pajares, J.M. (2005) Systematic review and meta-analysis: is 1-week proton pump inhibitor-based triple therapy sufficient to heal peptic ulcer?. *Alimentary Pharmacology and Therapeutics,* v.21, pp. 795 – 804.

Goldin, G.F. and Peura, D.A. (1996) Stress-related mucosal damage: What to do or not to do. *Gastroenterology clinics of North America,* v.6, pp. 505 – 526.

Graham, D.Y., Agrawal, M., Donald, R.C. (2002) Ulcer prevention in long-term users of non-steroidal anti inflammatory drugs: Results of a double-blind, randomised, multicenter, active and placebo-controlled study of misoprostol vs. lansoprazole. *Archives Internal Medicine*, v.162, pp. 169 - 175.

Graham, D.Y., Smith, J.L. and Dobbs, S.M. (1983) Gastric adaptation occurs with aspirin administration in man. *Digestive diseases and sciences,* v.28, pp. 1 – 6.

Graumlich, J.F. (2001) Preventing gastrointestinal complications of NSAIDs. *Postgrad. Med.*, v.109, pp. 117 - 128.

Griffin, M.R., Piper, J.M., Daugherty, J.R., Snowden, M. and Ray, W.A. (1991) Non-steroidal anti-inflammatory drug use and increased risk for peptic ulcer disease in elderly persons. *Annals internal Medicine, v.*114, pp. 257 - 263.

Griffin, M.R., Ray, W.A. and Schaffner, W. (1988) Nonsteroidal anti-inflammatory drug use and death from peptic ulcer in elderly persons. *Annals of Internal Medicine,* v.109, pp. 359 – 363.

Gunshefski, L., Flancbaum, L., Brolin, R.E. and Frankel, A. (1990) Changing patterns in perforated peptic ulcer disease. *American Journal of Surgery, v.*56, pp. 270 - 274.

Gy Pécsi and Rácz, (2004) The causes of acute upper GI bleedings of non-variceal origin yesterday and today. Z Gastroenterol., v.42.

H

Hallas, J., Lauritsen, J., Villadsen, H. and Gram, L. (1995) Nonsteroidal anti-inflammatory drugs and upper gastrointestinal bleeding, identifying high-risk groups by excess risk estimates. *Scandinavian journal of gastroenterology*, v.30, pp. 438 – 444.

Halter, F., Tarnawski, A.S., Schmassmann, A. and Peskar, B.M. (2001) Cyclooxygenase 2-implications on maintenance of gastric mucosal integrity and ulcer healing: controversial issues and perspectives. *Gut,* v.49, pp. 443 - 453.

Hawkey, C.J. (1990) Non-steroidal anti-inflammatory drugs and peptic ulcers-Facts and figures multiply, but do they add up?. *British Medical Journal,* v.300, pp. 278 - 284.

Hawkey, C.J. (2000) Nonsteroidal anti-inflammatory drug gastropathy. *Gastroenterology,* v.119, pp. 521 - 535.

Hawkey, C.J. and Hudson, N. (1993) Mucosal injury induced by drugs, chemicals and stress In: *Bockus Gastroenterology. 5th* Edition Haubdch W., Schaffner F. (Eds). W.B. Saunders Co., p. 320.

Hawkey, C.J. and Karrasch, A. (1998) Omeprazole compared with misoprostol for ulcers associated with non-steroidal anti-inflammatory drugs. The omeprazole versus misoprostol for NSAID-induced ulcer management (OMNIUM) study group. *New England Journal of Medicine*, v.338, pp. 727 - 734.

Hawkey, C.J, Laine, L., Simon, T., Beaulieu, A., Maldonado-Cocco, J., Acevedo, E., Shahane, A., Quan, H., Bolognese, J. and Mortensen, E. (2000) Comparison of the effect of rofecoxib (a cyclooxygenase 2 inhibitor), ibuprofen, and placebo on the gastroduodenal mucosa of patients with osteoarthritis. A randomized, double-blind, placebocontrolled trial. *Arthritis and rheumatism-arthritis care and research,* v.43, pp. 370 – 377.

Hoftiezer, J.W., O'Laughlin, J.C. and Ivey, K.J. (1982) Effects of 24 hours of aspirin, Bufferin, paracetamol and placebo on normal human gastroduodenal mucosa. *Gut,* v.23, pp. 692 – 697.

Hooper, L., Brown, T., Elliott, R., Payne, K., Roberts, C. and Symmons, D. (2004) The effectiveness of five strategies for the prevention of gastrointestinal toxicity induced by non-steroidal anti-inflammatory drugs: systematic review. *British Medical Journal,* v.329, pp. 948 - 952.

Hunang, J.Q., Sridhar, S. and Hunt, R.H. (2002) Role of Helicobacter pylori infection and non-steroidal anti-inflammatory drugs in peptic-ulcer disease: a meta-analysis. *Lancet*, v.359, pp. 14 – 22.

Hunt, R.H. and Bazzoli, F. (2004) Should NSAID/low-dose aspirin takers be tested routinly for H.pylori infection and treated if positive? Implication for primary risk of ulcer and ulcer relapse after initial healing. *Alimentary Pharmacology and Therapeutic,* v.19, pp. 9 - 16.

I

Infoscan Services, (2000) Internal Analgesics Category, Total Food, Drug and Mass Merch, 52 weeks ending July 16, 2000. Plymouth Meeting, PA: Information Resources, Inc.

J

Ji, K.Y. and Hu, F.L. (2006) Interaction or relationship between Helicobacter pylori and non-steroidal anti-inflammatory drugs in upper gastrointestinal diseases. *World Journal of Gastroenterology*, v.12, pp. 3789 - 3792.

Jimenez, D., Martin, M.J., Pozo, D., Alarcon, C., Esteban, J. and Brusighini, L. (2002) Mechanisms involved in protection afforded by L-Arginine in ibuprofeninduced gastric damage: Role of nitric oxide and prostaglandins. *Digestive diseases and sciences,* v.47, pp. 44 - 53.

K

Kaufman DW, Sheehan, J., Koff, R.S. Kelly, J.P., et al. The risk of acute major upper gastrointestinal bleeding among users of aspirin and ibuprofen at various levels of alcohol consumption. Am J Gastroenterol November 1999; 94:3189-96.).

Kelly, J.P., Kaufman, D.W., Jurgelon, J.M., Sheehan, J., Koff, R.S. and Shapiro, S. (1996) Risk of aspirin-associated major upper-gastrointestinal bleeding with enteric-coated or buffered product. *Lancet,* v.348, pp. 1413 – 1416.

Kikkawa, A., Iwakiri, R. and Ootani, H. (2005) Prevention of the rehaemorrhage of bleeding peptic ulcers: effects of Helicobacter pylori eradication and acid suppression. *Alimentary Pharmacology and Therapeutics,* v.21, pp. 79 – 84.

Koness, R.J., Cutitar, M. and Burchard, K.W. (1990) Perforated peptic ulcer: Determinants of morbidity and mortality. *American Journal of Surgery*, v.56, pp. 280 - 284.

Kubes, P., Zusuki, P. and Granger, D.N. (1991) Nitric oxide: An endogenous modulator of leukocyte adhesion. *Proceedings of National Academy Society of USA*, v.88, pp. 4651 - 4655.

Kurahur, K. and Matuhot, M. (2001) Clinical and endoscopic features of non-steroidal anti-inflammatory drug-induced colonic ulceration. *American Journal of Gastroenterology, v.96,* pp. 473 - 480.

Kurata, J.H. and Abbey, D.E. (1990) The effect of chronic aspirin use on duodenal and gastric ulcer hospitalizations. *Journal of clinical gastroenterology,* v.12, pp. 260 – 266.

Kuyvenhoven, J. P.H., Veenendaal, R. A. and Vandenbroucke, J. P. (1999) Peptic Ulcer Bleeding: Interaction between Non-Steroidal Anti-inflammatory Drugs, *Helicobacter pylori* Infection, and the ABO Blood Group System. *Scandinavian journal of gastroenterology,* v.34, pp. 1082 - 1086.

L

Labenz, J., Blum, A.L., Bolten, W.W., Dragosics, B., Rosch, W. and Stolte, M. (2002) Primary prevention of diclofenac associated ulcers and dyspepsia by omeprazole or triple therapy in Helicobacter pylori positive patients: A randomized, double blind, placebo controlled, clinical trial. *Gut,* v.51, pp. 329 - 335.

Labenz, J., Peitz, U., Kohl, H., Kaser, J., Malfertheiner, P., Hackelsberer, A. and Borsch, G. (1999) Helicobacter pylori increase the risk of peptic ulcer bleeding: a case-control study. *Ital J Gastroenterol Hepatol.* v.31, pp. 110 – 115.

Laheji, R.J., H.Straatman, J.B., Jansen, S.L. and Verbeek, A.L. (1998) Evaluation of commercially available Helicobacter pylori kits: a review. *Journal of clinical Microbiology,* v.36, pp. 2803 – 2809.

Laheji, R.J.F., Sturkenboom, M.C.J.M., Hassing, R.J., Dieleman, J., Stricker, B.H.C. and Jansen, J.B.M.J. (2004) Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. *Journal of American Medical Association*, v.292, pp. 1955 - 1960.

Lai, K.C., Lam, S.K. and Chu, K.M. (2002) Lansoprazole for the prevention of recurrences of ulcer complications from long-term low-dose aspirin use. New England Journal of Medicine, v.346, pp. 2033 - 2038.

Lai, K.C., Lam, S.K. and Chu, K.M. (2003) Lansoprazole reduces ulcer relapse after eradication of Helicobacter pylori in nonsteroidal anti-inflammatory drug users--a randomized trial. *Alimentary Pharmacology and Therapeutics, v.*18, pp. 829 - 836.

Laine, L. (1996) Nonsteroidal anti-inflammatory drug-gastropathy. *Gastro enterology clinics of North America,* v.6, pp. 489 – 504.

Laine, L. (2002) The effect of Helicobacter pylori infection on nonsteroidal anti-inflammatory drug-induced upper gastrointestinal tract injury. *Alimentary Pharmacology and Therapeutics, v.*16, pp. 34 - 39.

Laine, L., Harper, S., Simon, T., Bath, R., Johanson, J., Schwartz, H., Stern, S., Quan, H. and Bolognese, J. (1999) A randomized trial comparing the effect of rofecoxib, a COX-2 specific inhibitor, to ibuprofen on the gastroduodenal mucosa of osteoarthritis patients. *Gastroenterology,* v.117, pp. 776 – 783.

Lanas, A., Bajador, E. and Serrano, P. (2000) Nitrovasodilators, low-dose aspirin, other Nonsteroidal anti inflammatory drugs, and the risk of upper gastrointestinal bleeding. *New England Journal of Medicine, v.*343, pp. 834 - 839.

Langman, W.S., Brooks, P., Hawkey, C.J., Silverstein, F. and Yeomans, N. Working party Report to the World Congress of Gastroenterology, Sydney, 1990. Non-steroidal anti-inflammatory drug associated ulcer: Epidemiology, causation and treatment. *Journal of Gastroenterology and Hepatology,* v.6, pp. 442 - 449.

Lanza, F.L. (1989) A review of gastric ulcer and gastroduodenal injury in normal volunteers receiving aspirin and other non-steroidal anti-inflammatory drugs. *Scandinavian journal of gastroenterology,* v.24, pp. 24 – 31.

Leufkens, H.G., Urquart, J., Stricker, B.H.C., Acker, A. and Petri, H. (1992) Channeling of controlled release formulation of ketoprofen (Oscorel) in patients with history of gastrointestinal problems. *Journal of epidemiology and community health,* v. 46, pp. 428 - 432.

Lichtenberger, L.M., Romero, J.J. and Fox, J.G. (1997) Alterations in gastric surface hydrophobicity and phospholipids in the *Helicobacter felis* infected mouse. *Gastroenterology, v.*112, pp. 199 - 204.

Lo, C.C., Hsu, P.I. and Lo, G.H. (2006) Comparison of hemostatic efficacy for epinephrine injection alone and injection combined with hemoclip therapy in treating high-risk bleeding ulcers. *Gastrointestinal Endoscopy*, v.63, pp. 767 – 773.

Loren, L. (2001) Approaches to Nonsteroidal Anti-inflammatory Drug Use in the High-Risk Patient. *Gastroenterology*, v.120, pp. 594 – 606.

Loren, L. (2003) Serious lower gastrointestinal clinical events with non-selective NSAIDs and COXIB use. *Gastroenterology*, v.124, pp. 288 - 292.

Lucker, P.W., Pawlowski, C., Friedrich, I., Faiella, F. and Magni, E. (1994) Double-blind, randomised, multicentre clinical study evaluating the efficacy and tolerability of nimesulide in comparison with etodalac in patients suffering from osteoarthritis of the knee. *European Journal of Rheumatology & Inflammation,* v.14, pp. 29 - 38.

M

MacDonald, T.M., Morant, S.V., Robinson, G.C., Shield, M.J., McGilchrist, M.M., Murray, F.E. and McDevitt, D.G. (1997) Association of upper gastrointestinal toxicity of non-steroidal anti-inflammatory drugs with continued exposure: cohort study. British Medical Journal, v.315, pp. 1333 – 1337.

Malaty, H.M., Engstrand, L., Pedersen, N.L. and Graham, D.Y. (1994) *Helicobacter pylori* infection-genetic and environmental influences: A study of twins. *Annals of Internal Medicine*, v.120, pp. 982 - 986.

Manucherhr, K., Haleh, F., Ebrahim, F. and Masoud, E.A. (2007) Significant Upper Gi – Bleeding In Critically Ill Patients*. Journal of Gastroenterology.* v.5, pp. 2 - 8.

Marotta, F., Tajiri, H., Safran, P., Fesce, E. and Ideo, G. (1999) *Digestion, v.60, pp. 538 – 543.*

Martindale, R.G. (2005) Contemporary strategies for the prevention of stress-related mucosal bleeding. *American Journal of health-system pharmacy,* v.62, pp. 11 - 17.

Mashimo, H. M. Wu, D.C., Podolasky, D.K. and Fishman, M.C. (1995) Impaired defenses of intestinal mucosa in mice lacking in intestinal foil peptides. *Science*, v.274, pp. 262 -265.

May, G.R., Grook, P., Moore, K.P. and Page, C.P. (1991) The role of nitric oxide as endogenous regulator of platelet and neutrophile activation within the pulmonary circulation in the rabbit. *British journal of pharmacology*, v.102, pp. 759 - 763.

Messer, J., Reitman, D., Sacks, H.S., Smith, H. and Chalmers, T.C. (1983) Association of adrenocorticosteroid therapy and peptic-ulcer disease*. New England Journal of Medicine,* v.309, pp. 21 - 24.

Micheal, M.W. (1998) Future trends in the development of safer NSAIDs. *American journal of Medicine, v.*15, pp. 44S - 52S.

Morgan, D. (2002) Intravenous proton pump inhibitors in the critical care setting. *Critical Care Medicine*, v.30, pp. 369 - 372.

Morris, A.J., Madhock, R. and Stturock, R.D. (1991) Endoscopic diagnosis of small bowel ulceration in patients taking NSAIDs. *Lancet*, v.337, pp. 520 - 524.

Murphy, M.S. (1998) Growth factors and the gastrointestinal tract. *Nutrition, v.*14, pp. 771 - 774.

Muscara, M.N. and Wallace, J.L. (1999) Nitric oxide V: Therapeutic potential of nitric oxide donors and inhibitors. *American Journal of Physiology-gastrointestinal and liver physiology, v.* 276, pp. 1313 - 1316.

Mutlu, G.M., Mutlu, E.A. and Factor, P. (2001) GI complications in patients receiving mechanical ventilation. *Chest,* v.119, pp. 1222 – 1241.

N

Neal M. D. (1999) Sustained Release and Enteric Coated NSAIDs: Are They Really GI Safe?. *Journal of Pharm Pharmaceut Science,* v.2, pp. 5 – 14.

Nonprescription Drug Advisory Committee Meeting, September 2002 transcripts located and available at www.fda.gov/ohrms/dockets/ac/02/transcripts/3882T1.htm; last assessed 6 September 2007.

Nonprescription drugs USA, (1999) Internal Analgesics Product Category. Little Falls, NJ: Kline and Company.

O

Ofman, J.J., Maclea,n C.H., Straus, W.L. Morton, S.C., Berger, M.L. and Roth, E.A. (2003) Meta-analysis of dyspepsia and nonsteroidal anti-inflammatory drugs. *Arthritis Rheum,* v.49, pp. 508 - 518.

Okan, A., Tankurt, E., Aslan, B.U., Akpinar, H., Simsek, I. and Gonen, O. (2003) Relationship between non-steroidal anti-inflammatory drug use and Helicobacter pylori infection in bleeding or uncomplicated peptic ulcers: a case-control study. *J Gastroenterology Hepatol, v.*18, pp. 18 – 25.

O'Laughlin, J.C., Hoftiezer, J.W. and Ivey, K.J. (1981) Effect of aspirin on the human stomach in normals: endoscopic comparison of damage produced one hour, 24 hours, and 2 weeks after administration. *Scandinavian Journal of Gastroenterology*, v.16, pp. 211 – 214.

Oliver, B., Lindsay, A. D., William, R. M., Mary, B. and Jill, P. (1997) Acute upper gastrointestinal haemorrhage in west of Scotland: case ascertainment study. *British Medical Journal*, v.315, pp. 510 – 514.

P

Papatheodoridis, G.V. and Archimandritis, A.J. (2005) Role of Helicobacter pylori in aspirin or non-steroidal anti-inflammatory drug users. *World Journal of Gastroenterol*ogy, v.11, pp. 3811 - 3816.

Paulsen, G.A., Baigun, S., De Figueiredo, J. and Gomes, D.F. (1991) Efficacy and tolerability comparison of etodolac and piroxicam in the treatment of patients with osteoarthritis of the knee. *Current Medical Research & Opinion*, v.12, pp. 401 - 412.

Peura, D.A. (2004) Prevention of nonsteroidal anti-inflammatory drug - associated gastrointestinal symptoms and ulcer complication. *American Journal of Medicine*, v.117, pp. 63S – 71S.

Pilotto, A., Leandro, G., DiMario, F., Franceschi, M., Bozzola, L. and Valerio, G. (1997) Role of Helicobacter pylori infection on upper gastroinetestinal bleeding in the elderly: a case-control study. *Dig Dis Sci* , v.42, pp. 586 – 591.

Q

R

Raskin, J.B. (1999) Gastrointestinal effects of NSAID therapy. *American Journal of Medicine,* v.106, pp. 3 - 12.

Retail and Provider Perspective, (2000) *National Prescription Audit*, 1999–2000. Plymouth, PA: IMS Health.

Robert, A., Nezamis, J.E., Lancaster, C. and Hanchar, A.J. (1979) Cytoprotection by prostaglandins in rats: Prevention of gastric necrosis produced by alcohol, HCL,NaOH, hypertonic NaCL and thermal injury. *Gastroenterology*, v.77, pp. 433 - 443.

Robyn, T. (1997) Unnecessary prescribing of NSAIDs and the management of NSAID-related gastropathy in medical practice. *Ann Intern Med.*, v.127, pp. 429 -438.

Rogind, H. (1997) Comparison of etodolac and piroxicam in patients with osteoarthritis of the hip or knee: A prospective, randomised, double-blind, controlled multi-centre study. *Clinical Drug Investigation*, v.13, pp. 66 - 75.

S

Samuel, B. *Campylobacter* and *Helicobacter* (1996) *Medical Microbiology*, 4th ed.

Santolaria, S., Lanas, A., Benito, R., Perez-Aisa, M.A., Montoro, M. and Sainz, R. (1999) Helicobacter pylori infection is a protective factor for bleeding gastric ulcer but not for bleeding duodenal ulcers in NSAID users. *Aliment Pharmacol Ther, v.*13, pp. 1511 – 1518.

Sarosiek, J., Slomiani, A. and Slomiani, B.L. (1988) Evidence of weakening of gastric mucus integrity by Campylobacter pylori. *Scandinavian Journal of Gastroenterology*, v.23, pp. 585 - 590.

Satarasinghe, R.L. and Jayamaha, D.H. (2000) An audit on the prescription habits of non-steroidal anti-inf lammatory drugs (NSAIDS) in the medical clinics of a Base Hospital in Sri Lanka. *Journal of the Ceylon College of Physicians,* v.33, pp. 23 – 32.

Savon, J.J., Allen, M.L., DiMarino, A.J., Hermann, O.A. and Krum, R.P. (1995) Gastrointestinal blood loss with low dose (325 mg) plain and enteric-coated aspirin administration. *American Journal of Gastrology, v.*90, pp. 581 - 585.

Schaverbeke, T., Broutet, N., Zerbib, F., Combe, B., Bertin, P. and Lamouliatte, H. (2005) Should we eradicate Helicobacter pylori before prescribing an NSAID? Results of a placebo-controlled study. *American Journal of Gastroenterology*, v.100, pp. 2637 - 2643.

Scheiman, J.M. Andekar, R.R., Chernew, M.E. and Fendrick, A.M. (2001) Helicobacter pylori screening for individuals requiring chronic NSAID therapy: A decision analysis. *Alimentary Pharmacology and Therapeutics,* v.15, pp. 63 - 71.

Schnitzer, T.J., Ballard, I.M., Constantine, G. and McDonald, P. (1995) Double-blind, placebo-controlled comparison of the safety and efficacy of orally administered etodolac and nabumetone in patients with active osteoarthritis of the knee. *Clinical Therapeutics*, v.17, pp. 602 - 612.

Schnitzer, T.J., Burmester, G.R. and Mysler, E. (2004) Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), reduction in ulcer complications: randomized controlled trial. *Lancet*, v.364, pp. 665 - 674.

Serrano, P., Lanas, A., Arroyo, M.T., Casasnovas, J.A. and Ferreira, I. (2000) Risk stratification of upper gastrointestinal bleeding in cardiovascular patients on low-dose aspirin. A cohort study (abstr). *Gastroenterology*, v.118, pp. 862 – 866.

Silverstein, F., Faich, G., Goldstein, J.L., Simon, L.S., Pincus, T.P., Whelton, R., Eisen, G., Agrawal, N.M., Stenson, W.F., Burr, A.M., Zhao, W.W., Kent, J.D., Lefkowith, J.B., Verburg, K.M. and Geis, S.G. (2000) Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis. The CLASS study: a randomized controlled trial. *Journal of American Medical Association,* v.284, pp. 1247 – 1255.

Silverstein, F.E., Graham, D.Y., Senior, J.R., Davies, H.W., Struthers, B.J., Bittman, R.M. and Geis, G.S. (1995) Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving non-steroidal anti-inflammatory drugs-A randomized, double blind, placebo-controlled trial. *Annals Internal Medicine,* v.123, pp. 241 – 249.

Simon, L.S., Weaver, A.L. and Graham, D.Y. (1999) Anti-inflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis. *Journal of American Medical Association*, v.282, pp. 1921 - 1928.

Simon, L.S., Weaver, A.L., Graham, D.Y., Kivitz, A.J., Lipsky, P.E., Hubbard, R.C., Isakson, P.C., Verburg, K.M., Yu, S.S., Zhao, W.W. and Geis, G.S. (1999) Anti-inflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis: A randomized controlled trial. *Journal of American Medical Association,* v.282, pp. 1921 – 1928.

Singh, G. (1998) Recent considerations in non-steroidal anti-inflammatory drug gastropathy. *American Journal of Medicine,* v.105, pp. 31S - 38S.

Singh, G. and Ramey, D.R. (1998) NSAID induced gastrointestinal complications: the ARAMIS perspective–1997. *Journal of rheumatology*, v.51, pp. 8 – 16.

Slattery, J., Warlow, C.P., Shorrock, C.J. and Langman, M.J.S. (1995) Risks of gastrointestinal bleeding during secondary prevention of vascular events with aspirin—analysis of gastrointestinal bleeding during the UK-TIA trial. *Gut,* v.37, pp. 509 – 511.

Smalley, W.E., Ray, W.A., Daugherty, J.R. and Griffin, M.R. (1995) Nonsteroidal anti-inflammatory drugs and the incidence of hospitalizations for peptic ulcer disease in elderly persons. *American Journal of Epidemiology,* v.141, pp. 539 – 545.

Somerville, K., Faulkner, G. and Langman, W.S. (1986) Non-steroidal anti-inflammatory drugs and bleeding peptic ulcer. *Lancet, v.*1, pp. 462 - 464.

Sprit, M.J. (2003) Stress-related mucosal disease: risk factors and prophylactic therapy. *Clinical Therapeutics,* v.26, pp. 197 - 209.

Stack, W.A., Atherton, J.C., Hawkey, G.M., Logan, R.F.A. and Hawkey, C.J. (2002) Interactions between Helicobacter pylori and other risk factors for peptic ulcer bleeding. *Aliment Pharmacol Ther*, v.16, pp. 497 – 506.

Statistics Canada. Catalogue 82-003S1. Hospital Morbidity, 1989-90. Health Reports. 1992; 4(Suppl 1):34.

Sterioff, S., Orringer, M.B. and Cameron, J.L. (1974) Colon perforations associated with steroid therapy. *Surgery*, v.75, pp. 56 - 58.

Stollman, N. and Metz, D.C. (2005) Pathophysiology and prophylaxis of stress ulcer in intensive care unit patients. *Journal of critical care,* v.20, pp. 35 – 45.

T

Taha, A.S., Angerson, W., Nakshabendi, I., Beekman, H., Morran, C. and Sturrck, R.D. (1993) Gastric and duodenal mucosal blood flow in patients receiving nonsteroidal anti-inflammatory drugs-influence of age, smoking, ulceration and Helicobacter pylori. *Alimentary Pharmacology and Therapeutics*, v.7, pp. 41 - 45.

Talley, N.J., Evans, J.M., Fleming, K.C., Harmsen, W.S., Zinsmeister, A.R. and Melton, L.J. (1995) Nonsteroidal anti-inflammatory drugs and dyspepsia in the elderly. *Digestive diseases and sciences*, v.40, pp. 1345 – 1350.

Tamblyn, R. (1997) Unnecessary prescribing of NSAIDs and the management of NSAID-related gastropathy in medical practice. *Annals of Internal Medicine*, v.127, pp. 429 - 438.

Thompson, J.S. (1995) The intestinal response to critical illness. *American Journal of Gastroenterology*, v.90, pp. 190 - 200.

Tries, S., Neuper, T.W. and Laufer, S. (2002) The mechanism of action of new compound ML: 3000 (locofelone). Inhibition of 5-LO COX-1, and COX-2. *Inflammation research,* v.51, pp. 135 - 143.

U

V

Vergara, M., Catalan, M., Gisbert, J.P. and Calvet, X. (2005) Meta-analysis: Role of Helicobacter pylori eradication in the prevention of peptic ulcer in NSAID users. *Alimentary Pharmacology and Therapeutic, v.*21, pp. 1411 - 1418.

Viala, J., Chaput, C., Boneca, I.G., Cardona, A., Girardin, S. E., Moran, A. P., Athman, R., Memet, S., Huerre, M. R., Coyle, A.J., DiStefano, P.S., Sansonetti, P.J., Labigne, A., Bertin, J., Philpott, D. J. and Ferrero, R.L. (2004). Nod1 responds to peptidoglycan delivered by the Helicobacter pylori cag pathogenicity island. *Nature reviews Immunology,* v.5, pp. 1166 – 1174.

Vikas, D., Sindhu, S., Swati, A. C., Kuljeet, S. and Anand, K. (2003) Non-steroidal Drug-induced Gastrointestinal Toxicity: Mechanisms and Management. *Journal of investigational allergology and clinical immunology,* v.4, pp. 315 – 322.

W

Wallace, J.L. and Granger, D.N. (1996) The cellular and molecular basis of gastric mucosal defence. *Faseb journal*, v.10, pp. 731 - 740.

Warshaw, A.L., Welch, J.P. and Ottinger, L.W. (1976) Acute perforation of the colon associated with chronic corticosteroid therapy. *American Journal of Surgery,* v.131, pp. 442 - 446.

Webb, P.K., Conant, M.A. and Maibach, H.I. (1982) Perforation of the colon in high-dose corticosteroid therapy of pemphigus. *Journal of American the academy of Dermatology,* v.6, pp. 1040 -1041.

Weil, J., Colin-Jones, D., Langman, M., Lawson, D., Logan, R., Murphy, M., Rawlins, M., Vessey, M. and Wainwright, P. (1995) Prophylactic aspirin and risk of peptic ulcer bleeding. *British Medical Journal,* v.310, pp. 827 – 830.

Weiner, H.L., Rezai, A.R. and Cooper, P.R. (1993) Sigmoid diverticular perforation in neurosurgical patients receiving high-dose corticosteroids. *Neurosurgery*, v.33, pp. 40 - 43.

Whittle, B.J. and Lopez-Belmonte, J. (1993) Actions and interactions of endothelins, prostacyclin and nitric oxide in the gastric mucosa. *Journal of Physiology and Pharmacology, v.*44, pp. 91 - 107.

Wilcox, C. (1994) Striking prevalence of over-the-counter non-steroidal anti-inflammatory drug use in patients with upper gastrointestinal hemorrhage. *Archives of Internal Medicine, v.*154, pp. 42 - 46.

Williams, P.I., Hosie, J. and Scott, D.L. (1989) Etodolac therapy for osteoarthritis: a double-blind, placebocontrolled trial. *Current Medical Research and Opinion,* v.11, pp. 463 - 470.

Wu, C.Y., Poon, S.K., Chen, G.H., Chang, C.S. and Yeh, H.Z. (1999) Interaction between Helicobacter pylori and non-steroidal anti-inflammatory drugs in peptic ulcer bleeding. *Scand J Gastroenterol* , v.33, pp. 234 – 237.

X

Y

Yeoman, N.D. (2001) Approaches to healing and protection of NSAID induced ulcers. *American journal of Medicine*, v.110, pp. 24S - 28S.

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APPENDIX

- A: Proforma – Study on drug-induced UGI bleeding
- B: Master chart

Appendix A: Proforma – Study on Drug-induced UGI Bleeding

Department of Internal Medicine, Thanjavur Medical College

1. Name: **2.** Age: yrs **3.** Sex: M ☐ F ☐

4. IP No: **5**. Ward: **6**. Unit:

7. Occupation: **8.** Monthly income:

9. Height (in cm)_____ **10.** Weight (in Kg) _____ **11.** BMI _____

12. Hematemesis and malena

S.No.	History	Details
(a).	No. of times blood vomited	
(b).	Date and time of Hematemesis	
(c).	Quantity of blood loss each time (in milli litre)	(1) (2) (3) (4) (5) (6)
(d).	Total quantity of blood loss	(1)< 100ml ❒ (2)100 to 1000ml ❒ (3)>1000ml ❒
(e).	H /o Malena	
(f).	Past H/o Hematemesis / Malena	

13. Other symptoms

(a) Abdominal pain ⇨ (b) Heart burn ⇨

(c) Dysphagia ⇨ (d) Abdominal lump ⇨

(e) Waterbrash /vomiting ⇨ (f) Dyspepsia ⇨

(g) Jaundice ⇨ (h) Any other bleeding tendency ⇨

(i) Syncope ⇨ (j) Palpitation ⇨

14. Drug history

S.No.	Drug history	(a) Aspirin	(b) COX-1 Inhibitor	(c) COX-2 Inhibitor	(d) Others (specify)
1.	Strength of tablet				
2.	No. of tablets taken				
3.	Duration of intake				
4.	Prescribed or not?				
5.	Taken on empty stomach?				
6.	EC/SR?				
7.	Concomitant use of Gastro protective drug?				

15. Triggers

(a) Known PUD ☐ (b) Alcoholism ☐ (c) Smoking ☐ (d) Stress & SSI ☐

(e) Steroids ☐ (f) Anti coagulants ☐

16. Past history

(a) HT ☐ (b) DM ☐ (c) PT ☐ (d) CAHD ☐ (e) H/O Asthma/COPD ☐

(f) Others (Specify) _____

17. Clinical examination

(a) Oriented ☐ (b) Dyspnea ☐ (c) Pallor ☐ (d) Icterus ☐ (e) Pedal edema ☐

(f) Purpura/Petechiae ☐ (g) Pale, Sweaty extremities ☐ (h) Signs of liver failure ☐

(i) Sternal tenderness ☐ (j) RT aspiration showing GI bleed ☐ (k) PR for malena ☐

18. Vital signs

(a) Pulse: /min (b) BP (supine): mmHg (c) BP (standing): mmHg

(d) Respiratory rate: /min (e) Temp: ℃

19. Examination of systems:

(a) Abdomen :

(b) Respiratory system :

(c) Cardiovascular system :

(d) Central Nervous System :

20. Investigations:

(i) Urine: (a) Albumin ☐ (b) Sugar ☐ (c) Bile salt ☐ (d) Bile pigment ☐

(ii) CBC (a) Hb: (b) TC: (c) DC: P L M E B

(d) RBC: (e) Platelet

(iii) Blood(a) Group: (b) Bleeding time: (c) Clotting time:

(d) Bl.urea: (e) Bl.sugar(R): (f) Sr.Creatinine:

(g) Sr.Na+: (h) Sr.K+

(iv) LFT: (a) SGOT (b) SGPT (c) Sr.Bilirubin (d) Alk. Phosphatase

(e) Sr. Protein (f) Sr. Albumin

(v) Chest X-Ray:

(vi) ECG:

21. Test for H.Pylori (anti H.pylori IgG):

22. Upper GI Endoscopy: MGE No.: Date:

(a) Oesophagus:

(b) Stomach:

(c) Duodenum:

Appendix B: Master Chart

S.No.	1.Patient name	2. Age	3. Sex	4. IP No.	11. BMI	12. Hematemesis Malena				14. Drug name	14. Drug history							15. Triggers						16. Past history					17. No. of risk factors
						No. of times	Total blood loss	Malena?	Past History?		Strength of tablet	No .of tablets	Duration D / W / Mo	OTC?	Empty stomach	EC / SR ?	Non- use of GPA	Known PUD	Alcoholism	Smoking	Stress & SSI	Steroids	Anti coagulants	HT	DM	PT	CAHD	Asthma/COPD	
1.	Pitchaikannu	84	M	953160	21.4	3	2	Y	N	Aspirin	150	180	6Mo	N	N	N	N	N	N	Y	Y	Y	Y	Y	N	N	Y	N	7
2.	Ramalingam	62	M	953397	23.6	1	1	N	N	Ibuprofen	400	6	2D	Y	N	N	N	N	Y	Y	N	N	N	N	Y	N	N	N	3
3.	Govindharaj	50	M	946554	24.4	2	2	Y	N	Diclofenac	100	10	5D	Y	N	N	Y	N	Y	N	N	N	N	N	N	N	N	N	4
4.	Shajahan	63	M	945403	31.1	1	1	Y	N	Aspirin	150	90	3Mo	N	N	N	N	N	Y	Y	N	N	N	Y	Y	N	Y	N	4
5.	Sudhakar	25	M	951573	22.4	3	2	Y	N	Nimesulide	100	3	1D	N	N	N	Y	N	Y	N	N	N	N	N	N	N	N	N	2
6.	Gowri	45	F	951537	23.2	2	3	Y	N	Diclofenac	100	4	2D	Y	Y	Y	Y	Y	N	N	N	N	N	N	N	N	N	N	3
7.	Venkatachalam	50	M	944412	23.3	1	2	N	N	Heparin/Aspirin	150	4	4D	N	Y	N	N	N	N	Y	Y	Y	Y	N	Y	N	Y	Y	5
8.	Suresh	25	M	945253	22.8	1	1	N	N	Diclofenac	50	2	1D	N	Y	N	Y	N	Y	N	N	N	N	N	N	N	N	N	3
9.	Vellaiammal	50	F	946071	26.6	1	1	Y	N	Diclofenac	50	14	1W	Y	N	N	Y	Y	N	N	N	Y	N	N	N	N	N	Y	4
10.	Rajathi	28	F	889497	25.6	1	1	N	N	Ibuprofen	400	10	4D	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	1
11.	Antony samy	70	M	889576	19.6	2	2	Y	N	Nimesulide	100	6	3D	N	Y	N	N	N	N	Y	N	N	N	N	Y	N	N	N	3
12.	Ganesan	63	M	889719	25.3	1	1	N	N	Ibuprofen	400	8	3D	N	N	N	N	N	Y	Y	N	N	N	N	N	N	N	N	2
13.	Ramu	60	M	891427	24.1	2	2	Y	N	Indomethacin	250	4	2D	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	2
14.	Radha	50	F	900775	23.9	1	1	Y	N	Ibuprofen	400	6	2D	Y	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	3
15.	Shankar	67	M	901035	24.2	2	2	Y	N	Aspirin	150	90	3Mo	N	Y	N	N	N	Y	N	N	N	N	N	Y	N	Y	N	3
16.	Abirami	27	F	902656	20.3	1	1	N	N	Ibuprofen	400	5	2D	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	2
17.	Adhirai	68	F	904008	24.4	1	1	Y	N	Mefenamic acid	250	8	3D	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	2
18.	Panneerselvam	60	M	905804	25.4	2	1	Y	N	Aspirin	150	150	5Mo	N	N	N	N	N	N	Y	Y	N	N	N	Y	N	Y	N	3
19.	Arulmary	37	F	905351	21.4	1	1	N	N	Ibuprofen	400	4	2D	Y	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	2
20.	Tamilselvan	35	M	902920	28.2	1	1	N	N	Diclofenac	50	5	3D	Y	N	N	Y	N	Y	N	N	N	N	N	N	N	N	N	4
21.	Sarasu	59	F	903313	23.1	2	1	Y	N	Ibuprofen	200	15	6D	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	1
22.	Amutha	34	F	932387	25.3	2	1	Y	N	Ibuprofen	400	7	3D	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	1
23.	Sarasu	64	F	932287	23.7	1	1	N	N	Piroxicam	20	4	4D	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	2
24.	Selvendhran	28	M	932531	24.4	1	1	N	N	Diclofenac	50	5	3D	Y	Y	N	Y	N	N	Y	N	N	N	N	N	N	N	N	3
25.	Chandra	70	F	935141	22.3	2	2	Y	N	Ibuprofen	400	12	6D	Y	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	4

Note: (M) - Male; (F) - Female; (Y) –Yes; (N) – No; (Nl) - Normal; (+) - Findings present; (-) - Negative; (D) – Days; (W) – Weeks; (Mo) – Months;

Appendix B: Master Chart (Continued…)

S.No	1.Patient name	4. IP No.	18. vital signs			20. Investigations														21. H.pylori	22. UGI Endoscopy				
			Pulse rate	BP	Resp. rate	Urine. Alb	Urine. Sugar	Hb (g%)	TC	Platelet (lakh)	Blood Group	Bleeding time	Clotting time	Blood urea	Blood sugar	Sr.Creatinine	LFT	Chest X-Ray	ECG		MGE no.	Date	Oesophagus	Stomach	Duodenum
1.	Pitchaikannu	953160	90	130/90	18	-	-	9.6	7600	1.8	O+	3'05	5'20	36	107	1.4	Nl	Nl	+	-	1412/07	27/8/07	Nl	+	Nl
2.	Ramalingam	953397	78	130/86	15	-	+	9.2	7300	1.4	AB+	2'50	6'10	42	278	1.3	Nl	Nl	Nl	-	1441/07	30/8/07	Nl	+	Nl
3.	Govindharaj	946554	108	90/60	16	-	-	9.8	6500	1.1	O-	2'45	5'15	29	94	1.1	Nl	Nl	Nl	-	1257/07	28/6/07	Nl	+	+
4.	Shajahan	945403	112	120/84	17	-	-	10.2	10500	1.4	O+	3'00	6'30	35	125	1.1	Nl	+	+	-	1232/07	21/6/07	Nl	Nl	+
5.	Sudhakar	951573	88	124/84	15	-	-	8.2	4800	2.1	A+	2'50	6'20	37	108	0.9	Nl	Nl	Nl	-	1403/07	7/8/07	Nl	+	Nl
6.	Gowri	951537	90	11O/70	15	-	-	6.6	3600	1.5	A+	3.15	7'10	40	92	1.2	Nl	Nl	Nl	-	1396/07	2/8/07	Nl	+	+
7.	Venkatachalam	944412	106	134/70	16	-	-	7.6	6200	1.5	O-	3'50	6'00	38	106	1.0	Nl	+	+	-	1098/07	14/6/07	Nl	+	+
8.	Suresh	945253	100	96/66	16	-	-	8.7	7100	1.9	O+	2'45	5'15	35	98	1.6	Nl	Nl	Nl	-	1221/07	21/6/07	Nl	+	Nl
9.	Vellaiammal	946071	106	106/70	15	-	-	8.2	6200	1.7	AB+	2'40	5'30	33	72	0.9	Nl	+	+	-	1208/07	26/6/07	Nl	+	Nl
10.	Rajathi	889497	110	96/60	16	-	-	9.1	4900	1.6	AB-	4'10	5'40	29	115	0.9	Nl	Nl	Nl	+	1214/06	8/6/06	Nl	Nl	Nl
11.	Antony samy	889576	86	130/84	17	-	-	7.3	4300	1.4	O-	3'30	5'00	45	153	1.1	Nl	Nl	Nl	-	1229/06	8/6/06	Nl	+	Nl
12.	Ganesan	889719	108	130/80	16	-	-	10.1	6800	2.3	B+	3'45	4'50	41	84	1.3	Nl	Nl	Nl	-	1281/06	15/6/06	Nl	+	Nl
13.	Ramu	891427	120	100/74	18	-	-	9.3	6500	1.9	O+	2'45	5'15	39	79	0.8	Nl	Nl	Nl	-	1312/06	22/6/06	Nl	Nl	+
14.	Radha	900775	100	110/86	15	-	-	6.2	4100	1.7	O-	3'20	6'25	43	95	1.3	Nl	+	Nl	-	1386/06	29/6/06	Nl	+	Nl
15.	Shankar	901035	104	106/80	16	-	+	8.5	4300	1.8	AB+	2'50	5'30	37	198	1.1	Nl	Nl	Nl	-	1410/06	06/7/06	Nl	Nl	+
16.	Abirami	902656	88	124/88	16	-	-	6.4	4200	1.8	O+	1'55	7'20	45	132	1.4	Nl	Nl	Nl	-	1431/06	13/7/06	Nl	+	Nl
17.	Adhirai	904008	84	140/86	14	-	-	7.9	5700	2.0	O+	3'20	6'25	27	126	1.0	Nl	Nl	Nl	-	1450/06	20/7/06	Nl	+	Nl
18.	Panneerselvam	905804	102	130/88	18	-	+	9.6	7800	2.1	B-	3'30	5'45	36	297	0.9	Nl	Nl	+	-	1538/06	03/8/06	Nl	Nl	+
19.	Arulmary	905351	90	128/84	16	-	-	10.8	8900	2.5	B+	2'45	5'10	34	128	0.8	Nl	Nl	Nl	-	1491/06	03/8/06	Nl	Nl	Nl
20.	Tamilselvan	902920	94	134/80	15	-	-	9.2	7300	2.1	O+	2'30	5'10	42	89	1.3	Nl	Nl	Nl	-	1403/06	22/8/06	Nl	Nl	Nl
21.	Sarasu	903313	102	94/60	16	-	-	9.5	8100	2.2	A-	3'10	6'05	32	68	1.2	Nl	Nl	Nl	-	1437/06	29/8/06	Nl	Nl	+
22.	Amutha	932387	94	110/76	14	-	-	7.4	5100	1.8	O-	3'30	6'55	44	114	1.3	Nl	Nl	Nl	-	468/07	15/3/07	Nl	Nl	Nl
23.	Sarasu	932287	86	140/86	14	-	-	7.7	4400	1.5	B-	4'00	5'30	38	88	1.1	Nl	Nl	Nl	+	496/07	15/3/07	Nl	+	Nl
24.	Selvendhran	932531	108	122/86	16	-	-	6.9	5300	1.7	A+	2'55	6'10	23	113	1.0	Nl	Nl	Nl	-	517/07	20/3/07	Nl	+	Nl
25.	Chandra	935141	112	130/84	14	-	-	5.8	4900	1.6	O+	2'20	5'25	43	93	0.9	Nl	+l	Nl	-	640/07	12/4/07	Nl	+	Nl

Note: (M) - Male; (F) - Female; (Y) –Yes; (N) – No; (Nl) - Normal; (+) - Findings present; (-) - Negative; (D) – Days; (W) – Weeks; (Mo) – Months;

Appendix B: Master Chart (Continued…)

S.No.	1.Patient name	2. Age	3. Sex	4. IP No.	11. BMI	12. Hematemesis Malena				14. Drug name	14. Drug history							15. Triggers						16. Past history					17.No. of risk factors
						No. of times	Total Blood	Malena?	Past History?		Strength of tablet	No. of tablets	Duration D/W/Mo	OTC?	Empty stomach	EC / SR ?	Non use of GPA	Known PUD	Alcoholism	Smoking	Stress & SSI	Steroids	Anti coagulants	HT	DM	PT	CAHD	Asthma/COPD	
26.	Parimala	38	F	936210	23.2	2	1	Y	N	Ibuprofen	400	12	4D	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	1
27.	Karuppasamy	58	M	937309	22.8	3	1	Y	N	Aspirin	150	45	45D	N	N	N	N	N	Y	Y	Y	N	N	Y	Y	N	Y	N	4
28.	Kamalam	60	F	936006	27.9	2	2	Y	N	Diclofenac	50	8	3D	N	N	N	N	N	N	N	N	Y	N	N	Y	N	N	Y	1
29.	Sakkarapani	63	M	937262	24.6	4	2	Y	N	Indomethacin	25	20	12D	N	Y	N	N	Y	Y	Y	N	N	N	N	N	N	N	N	4
30.	Ravi	30	M	922409	23.7	2	1	Y	N	Nimesulide	100	8	3D	Y	N	N	Y	N	Y	N	Y	N	N	N	N	N	N	N	4
31.	Rathinasamy	65	M	937809	30.2	5	3	Y	N	Diclofenac	100	6	3D	Y	N	N	Y	N	Y	N	N	N	N	N	Y	N	N	N	4
32.	Elambal	70	F	938443	21.3	1	1	N	N	Ibuprofen	200	10	4D	Y	N	N	Y	Y	N	N	N	N	N	N	N	N	N	N	6
33.	Elangovan	40	M	938652	24.6	0	-	Y	N	Mefenamic acid	250	12	6D	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	2
34.	Swaminathan	65	M	934045	24.2	4	1	Y	N	Ibuprofen	400	15	5D	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	2
35.	Padharnisha	55	F	938301	23.6	5	3	Y	N	Diclofenac	75	12	6D	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	1
36.	Selvam	42	M	938828	23.6	2	2	Y	N	Nimesulide	100	10	5D	N	N	N	Y	N	Y	Y	N	N	N	N	N	N	N	N	4
37.	Sakeel ahmad	24	M	940106	30.8	2	3	Y	N	Ibuprofen	400	10	4D	N	Y	N	N	N	Y	N	N	N	N	N	N	N	N	N	2
38.	Gomathi	60	F	939020	22.1	1	1	N	N	Indomethacin	50	4	2D	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	1
39.	Arumugam	60	M	940901	22.9	1	1	N	N	Ibuprofen	400	8	3D	Y	N	N	Y	N	N	N	N	N	N	N	Y	N	N	N	2
40.	Jeyakkodi	61	F	940428	24.2	3	2	Y	N	Ibuprofen	200	10	4D	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	1
41.	Vanathiyan	23	M	940919	20.8	0	-	Y	N	Ibuprofen	200	4	2D	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	2
42.	Balakrishnan	57	M	941062	23.7	4	2	Y	N	Mefenamic acid	250	10	5D	N	N	N	N	N	Y	N	N	N	N	N	Y	N	N	N	2
43.	Murugan	60	M	941659	24.4	2	1	Y	N	Ibuprofen	200	18	1W	Y	N	N	Y	N	Y	Y	N	N	N	N	Y	N	N	N	5
44.	Karuppasamy	55	M	942081	21.8	4	2	Y	N	Aspirin	150	270	9Mo	N	N	N	N	N	N	N	Y	N	N	Y	Y	N	Y	N	2
45.	Raman	61	M	942219	25.2	1	1	N	N	Diclofenac	50	5	3D	Y	Y	N	Y	N	Y	N	N	N	N	N	N	N	N	N	4
46.	Pitchaiyan	50	M	942826	22.1	2	1	Y	N	Ibuprofen	400	25	10D	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	1
47.	Raman	61	M	943126	25.8	4	2	Y	N	Aspirin	150	60	2Mo	N	N	N	N	N	Y	N	N	N	N	Y	Y	N	Y	N	2
48.	Indirani	66	F	941849	23.7	2	1	Y	N	Indomethacin	25	14	1W	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	1
49.	Sami ayya	45	M	944443	24.4	0	-	Y	N	Diclofenac	50	10	5D	Y	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	3
50.	Vijayakumar	37	M	944909	27.6	2	2	Y	N	Ibuprofen	400	12	6D	N	N	N	N	N	Y	Y	N	N	N	N	N	N	N	N	2

Note: (M) - Male; (F) - Female; (Y) –Yes; (N) – No; (Nl) - Normal; (+) - Findings present; (-) - Negative; (D) – Days; (W) – Weeks; (Mo) – Months;

Appendix B: Master Chart (Continued…)

S.No	1.Patient name	4. IP No.	18. vital signs			20. Investigations													21. H.pylori	22. UGI Endoscopy				
			Pulse rate	BP	Resp. rate	Urine. Alb	Urine. Sugar	Hb (g%)	TC	Platelet (lakh)	Blood Group	Bleeding time	Clotting time	Blood urea	Blood sugar	Sr.Creatinine	LFT	Chest X-Ray	ECG		MGE no.	Date	Oesophagus	Stomach	Duodenum
26.	Parimala	936210	94	100/70	15	-	-	9.6	8600	1.5	O-	3'15	5'30	29	97	1.0	Nl	Nl	Nl	-	661/07	12/4/07	Nl	Nl	Nl
27.	Karuppasamy	937309	86	170/96	17	+	+	8.6	7800	1.6	O+	3'10	7'40	45	258	1.6	Nl	Nl	+	-	668/07	16/4/07	Nl	Nl	+
28.	Kamalam	936006	102	102/80	14	-	+	7.6	4800	1.4	B+	3'25	5'05	39	296	1.1	Nl	+	Nl	-	667/07	17/4/07	Nl	+	Nl
29.	Sakkarapani	937262	114	90/64	18	-	-	7.9	6300	1.8	O+	2'55	5'45	45	106	1.0	Nl	Nl	Nl	-	663/07	17/4/07	Nl	+	+
30.	Ravi	922409	110	120/80	16	-	-	7.2	5200	1.4	A+	3'10	6'05	52	91	1.3	Nl	Nl	Nl	-	619/07	19/4/07	Nl	+	Nl
31.	Rathinasamy	937809	120	96/60	18	-	+	6.2	4200	1.7	B+	3'35	6'15	42	152	1.0	Nl	Nl	Nl	-	654/07	19/4/07	Nl	Nl	+
32.	Elambal	938443	86	110/74	14	-	-	8.6	6200	1.4	O+	2'50	5'20	39	89	1.1	Nl	Nl	Nl	+	707/07	24/4/07	Nl	+	Nl
33.	Elangovan	938652	96	130/80	14	-	-	10.7	7400	2.3	O-	2'35	5'45	32	106	0.9	Nl	Nl	Nl	-	706/07	24/4/07	Nl	Nl	Nl
34.	Swaminathan	934045	86	136/84	15	-	-	9.2	6500	1.7	AB+	2'10	4'50	38	72	1.0	Nl	+	+	-	732/07	26/4/07	Nl	+	Nl
35.	Padharnisha	938301	110	94/64	20	-	-	6.1	4700	1.6	O+	3'50	5'50	39	104	1.0	Nl	Nl	Nl	-	736/07	26/4/07	Nl	+	Nl
36.	Selvam	938828	94	130/84	16	-	-	8.3	5100	2.2	O+	2'40	5'15	45	123	1.0	Nl	Nl	Nl	-	745/07	1/5/07	Nl	+	Nl
37.	Sakeel ahmad	940106	108	170/96	16	-	-	9.2	5200	1.9	B-	3'25	4'45	47	96	1.1	Nl	Nl	Nl	+	783/07	4/5/07	Nl	Nl	+
38.	Gomathi	939020	90	100/70	15	-	-	9.3	6500	1.7	B+	2'55	5'25	39	79	0.8	Nl	Nl	Nl	-	777/07	4/5/07	Nl	Nl	Nl
39.	Arumugam	940901	88	110/86	15	-	+	9.2	4900	1.6	AB-	3'30	6'25	43	230	1.2	Nl	Nl	+	-	815/07	8/5/07	Nl	+	Nl
40.	Jeyakkodi	940428	94	106/70	16	-	-	8.9	5300	2.1	O-	2'55	5'40	31	98	0.9	Nl	Nl	Nl	-	807/07	8/5/07	Nl	Nl	Nl
41.	Vanathiyan	940919	90	124/80	16	-	-	10.1	5800	1.9	B-	2'20	6'40	35	102	1.0	Nl	Nl	Nl	+	525/07	10/5/07	Nl	+	Nl
42.	Balakrishnan	941062	104	130/86	14	-	+	9.3	5700	1.8	O-	3'25	6'10	37	196	1.0	Nl	Nl	Nl	-	840/07	10/5/07	Nl	Nl	+
43.	Murugan	941659	96	140/86	18	-	+	9.5	8500	2.1	O+	3'10	5'15	36	207	0.9	Nl	Nl	Nl	-	843/07	17/5/07	Nl	+	Nl
44.	Karuppasamy	942081	90	138/84	16	-	+	8.8	6300	1.8	A+	2'55	5'20	39	223	1.0	Nl	Nl	+	-	876/07	22/5/07	Nl	+	Nl
45.	Raman	942219	96	124/86	15	-	-	9.3	7400	1.9	O+	2'35	5'20	42	94	1.2	Nl	Nl	+	-	889/07	22/5/07	Nl	Nl	Nl
46.	Pitchaiyan	942826	90	104/60	16	-	-	9.4	7100	1.8	AB+	3'20	5'40	39	72	1.0	Nl	Nl	Nl	-	936/07	24/5/07	Nl	Nl	Nl
47.	Raman	943126	94	150/76	14	-	+	8.6	5400	1.6	O-	3'50	6'55	44	214	1.1	Nl	Nl	+	-	939/07	29/5/07	Nl	+	+
48.	Indirani	941849	76	130/88	14	-	-	7.2	4400	1.3	B+	4'05	5'10	38	89	1.1	Nl	Nl	Nl	-	869/07	31/5/07	Nl	+	Nl
49.	Sami ayya	944443	98	126/86	16	-	-	9.9	6600	1.8	A+	2'45	6'00	33	118	1.0	Nl	Nl	Nl	+	995/07	7/6/07	Nl	Nl	+
50.	Vijayakumar	944909	92	120/84	14	-	-	8.8	4900	2.4	A+	2'35	5'25	41	98	0.9	Nl	Nl	Nl	-	983/07	12/6/07	Nl	+	Nl

Note: (M) - Male; (F) - Female; (Y) –Yes; (N) – No; (Nl) - Normal; (+) - Findings present; (-) - Negative; (D) – Days; (W) – Weeks; (Mo) – Months;